# *Probiotics in the Management of Genitourinary Tract and Gastrointestinal Tract Infections in Women*

*Donald Brown, ND*

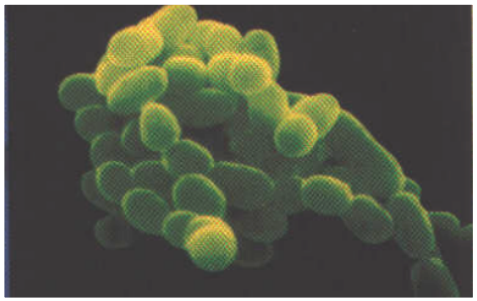
*January 28, 2012*

# *Vaginal Microbiota*
## *A little history*

- *In 1892, Albert Döderlein first described the vaginal bacillus as a long, thick, non-motile, gram-positive bacillus occurring in normal vaginal secretions. He considered the antagonistic action of the organism on the growth of staphylococci, and the bactericidal action to be due to lactic acid produced by the bacillus.*
- *In 1921, examining the vaginal flora of 288 non-pregnant women with vaginitis, Schröder described 3 grades based on vaginal secretions:*
  - *Grade I: only gram-positive vaginal bacillus and acidic*
  - *Grade II: Döderlein bacillus absent and various other organisms found*
  - *Grade III: Döderlein bacillus absent and a preponderance of micrococci, diphtheroids, and streptococci present with an alkaline discharge and many pus cells*

# *Vaginal Microbiota*

- *The estimated number of microbial species inhabiting the vagina are around 50 compared to 800 species in the gut*
- *Microbial flora of a healthy premenopausal woman is generally dominated by Lactobacillus species – most common are L. iners, L. crispatus, L. gasseri, L. jenesenii followed by L. acidophilus, L. fermentum, L. plantarum, L. brevis, L. casei. L. vaginalis, L. delbruekii, L. salivarius, L. reuteri, L. rhamnosus*



# *Vaginal Microbiota*

- ***Factors influencing the vaginal microflora include:***
  - ***Hormonal changes (particularly estrogen)***
    - ***Changes in microbiota during menstrual cycle***
    - ***Lactobacilli counts decrease during menopause but can vary greatly with vaginal or oral estrogen replacement***
  - ***Vaginal pH and glycogen content***
  - ***Use of topical microbicides***

# *Lactobacilli*
## *Protective Role in the Female GU Tract*

- *Inhibition of binding of potential pathogenic bacteria*
  - *Production of biosurfactants*
- *Production of weak antimicrobial substances including $H_2O_2$ to limit pathogen growth*
- *Immunomodulatory actions*
  - *Vaginal microflora regulates the epithelial innate immunity in a species- and strain-specific manner (mBio 2011;2(6):e00168-11)*

# *Lactobacilli*
## *Disruption of Urogenital Biofilms*

- *Uropathogenic E. coli and pathogens associated with bacterial vaginosis (G. vaginalis, Atopobium vaginae) form dense biofilms, permitting evasion of the host's immune system and impending antimicrobial access*
- *An in vitro study found that L. rhamnosus GR-1 and L. reuteri RC-14 are able to incorporate themselves into the pathogenic bioflims and cause disruption and some killing of the bacteria*
- *Metronidazole produced holes in G. vaginalis and A. vaginae biofilms but did not eradicate the organisms*

*Colloids Surfaces B: Biointerfaces 2011;86:58-64.*

# *Probiotics*
# *Female Genitourinary Tract Infections*

- ***Bacterial vaginosis***
- ***Vulvovaginal candidiasis***
- ***Urinary Tract Infections***

# *Probiotics for Vaginitis*
## *An early clinical trial*

- *A study completed in 1958 divided 165 women with vaginitis into "Plan A" or "Plan B". In Plan A, "with the speculum still in place, the entire contents of a culture tube [in skim milk], approximately 7 million Döderlein bacilli, were poured into the vagina. Group B received a lypholized powder reconstituted in glucose and water.*
- *Many women with vaginitis showed an absence of Döderlein bacilli. Administration of the Döderlein bacilli reduced symptoms of vaginitis and the organism was found to increase and become the predominant vaginal flora.*

*Am J Obstet Gynecol 1960:79:432-40.*

# *Probiotics for Female GU Infections*
## *What's the best route for administration?*

- *The assumption for many years (and continues in some circles) is that intravaginal application of probiotics is the preferred means to administer probiotics for treatment/prevention of GU infections*
- *Canadian researchers challenged this by isolating two vaginal strains – L. rhamnosus GR-1 and L. reuteri RC-14 (previously L. fermentum RC-14) and demonstrating vaginal colonization following oral administration to women (significant increase noted at days 28 and 60). Their data to date has been strongest in the treatment of BV.*

*FEMS Immunol Med Microbiology 2003;35:131-4.*
*J Clin Gastroenterol 2004;38:*

# *Bacterial Vaginosis*

- ***Associated with:***
  - ***Pelvic inflammatory disease***
  - ***Infections following gynecological surgery***
  - ***Increased risk of pre-term birth***
  - ***Increased risk of HIV infection***
  - ***High recurrence rate despite oral or intra-vaginal treatment with metronidazole or clindamycin***

# Bacterial Vaginosis
## Changes in Vaginal Microflora

- The presence of $H_2O_2$ producing Lactobacilli spp has been shown to be significantly higher in healthy women compared those with BV.[1]
- Vaginal lactobacilli were isolated from 73.7% of 825 women without BV, and from 29.8% of 131 with BV.[2]
- Another study with pregnant women (> 18 years old) found vaginal lactobacilli in 74.3% of 2729 women without BV and 38.4% of women with BV.[3]


1. *J Clin Microbiol* 1989;27:251-6.
2. *Arch Gynecol Obstet* 2001;265:11-15.
3. *Am J Obstet Gynecol* 1998;178:580-7.

# Bacterial Vaginosis
## Changes in Vaginal Microflora, cont.

- In Chinese women, healthy subjects had a higher concentration of *L. crispatus* compared to women with BV. *L. gasseri* was also higher in healthy women. *L. iners* was higher in women with BV.[1]
- In pregnant Japanese women, the presence of *L. crispatus, L. gasseri, L. jensenii* were higher in healthy subjects compared to those with BV. *L. iners* was associated with increased presence of BVAB2.[2]


1. *Chin Med J* 2009;122:2748-51.
2. *BMC Infectious Dis* 2007;7:128 (doi:10.1186/1471-2334-7-128)

# *Bacterial Vaginosis*
# *Adjunctive Treatment with Probiotics*

- *In a DBPCT, 125 premenopausal women (18-44 years old) with diagnosed BV received oral metronidazole (550 mg b.i.d.) from days 1 to 7 and then randomized to receive one capsule of L. rhamnosus GR-1 (1 x $10^9$) and L. reuteri RC-14 (1 x $10^9$) or placebo orally b.i.d. from days 1 to 30.*
- *In the antibiotic/probiotic group, 88% of women were cured compared to 40% in the antibiotic/placebo group ($p < 0.001$). Of the remaining antibiotic/ probiotic subjects (12%), none had BV, but had mild irritative symptoms, no discharge or odor, a weakly positive sialidase score and intermediate Nugent score. This contrasted with the remaining 34 antibiotic/placebo subjects, of which half had BV and the other half had an intermediate status.*

*Microbes Infection 2006;8:1450-4.*

# *Bacterial Vaginosis*
## *Adjunctive Treatment with Probiotics*

- *In a DBPCT, 64 premenopausal women with diagnosed BV received a single dose of tinidazole (2 g) and either one capsule of L. rhamnosus GR-1 (1 x $10^9$) and L. reuteri RC-14 (1 x $10^9$) or placebo orally b.i.d. from days 1 to 28.*
- *At day 28, the probiotic group had a higher cure rate (Nugent score and Amsel test) of BV compared to placebo (87.5% vs. 50%; p = 0.001).*
- *According to the Gram-stain Nugent score, more women in the probiotic group were assessed with "normal" vaginal microbiota compared to placebo (75% vs. 34.4%; p = 0.011).*

*Can J Microbiol 2009;55:133-8.*

# *Bacterial Vaginosis*
## *Adjunctive Treatment with Probiotics*

- *100 women (mean age 34 years) with bacterial vaginosis were treated with 2% vaginal clindamycin cream for 7 days and then randomized to receive capsules (vaginally inserted) containing either placebo or a combination of L. gasseri (Lba EB01-DSM 14869)* and L. rhamnosus (Lbp EB01-DSM 14870)* ($10^9$cfu per capsule) for 10 days. The above was repeated for 3 cycles. [*cultured from healthy women]*
- *Treatment with the probiotic combination did not improve the efficacy of BV treatment during the first month of treatment.*
- *However, women initially "cured" were followed for 6 menstrual cycles or until relapse within that time. At the end of 6 months, 64.9% of the probiotic-treated group were still BV-free compared to 46.2% in the placebo group ($p = 0.027$).*

*BMC Women's Health 2008;8:3 (doi: 10.1186/1472-6874-8-3)*

# *Bacterial Vaginosis*
## *Adjunctive Treatment with Probiotics*

- *190 women with BV treated with clindamycin were randomized to receive either vaginal capsules containing L. casei rhamnosus (Lcr 35; $10^9$ cfu) for 7 days after oral clindamycin or no treatment. The reduction in Nugent score (by at least 5 grades) was significantly higher in the probiotic group ($p < 0.001$).[1]*
- *DBPCT compared cure rate in women with BV following vaginal clindamycin treatment. During their next period, women were randomized to either a tampon "loaded" with L. fermentum, L. casei rhamnosus, L. gasseri or a "placebo" tampon. Cure rate was recorded at the next menstruation. There was no difference in cure rate between groups.[2]*


1. *BJOG* 2008;115:1369-74.
2. *Acta Derm Venerol* 2005;85:42-6.

# *BV and VVC*

## *Adjunctive Treatment with Probiotics*

- *In a DBPCT, 95 women (BV=39; VVC=45; both=11) following conventional treatment were randomized to receive a vaginal capsule containing L. gasseri LN40, L. fermentum LN99, L. casei rhamnosus LN113, P. acidilactici LN23 ($10^8$-$10^{10}$ cfu) or placebo for 5 days.*
- *Probiotic strains were present in vaginal cultures 2-3 days after administration (53% colonized after one menstruation). 93% of women in the probiotic group were cured after 2-3 days compared to 83% in the placebo group (78% vs. 71% after 1st menstruation).*
- *The probiotic group had significantly less malodorous discharge.*

*Mastromarino et al. (2010) 491-8*

# *Prevention of Spontaneous Pre-term Labor Associated with BV*

- *A large DBPCT Brazilian trial with 644 pregnant women with BV looked at the ability of L. rhamnosus GR-1 and L. reuteri RC-14 during the 24th to 26th weeks of gestation to decrease risk of spontaneous pre-term labor.*
- *The study failed to have a sample size sufficient to estimate statistically significant intent-to-treat effects.*

*Trials 2011;12:239 (doi: 10.1186/1745-6215-12-239)*

# *Vulvovaginal Candidiasis*

- *A 2000 survey in the U.S., found that 6.5% and 8% of women older than 18 years reported ≥ 1 and ≥ 4 episodes of VVC during he 2 months and 1 year prior to the survey. Total estimated annual cost was $1.8 billion.*[1]
- *Although the pathogenesis remains controversial, risk factors include:*
  - *Antibiotic therapy, spermicide use, oral contraceptives, estrogen therapy, diabetes mellitus, tight clothing, frequent sexual intercourse*

1. *Amer Sex Transm Dis Assoc* 2000;27:230-5.

# *Vulvovaginal Candidiasis*
## *Prevention of Recurrence with Probiotics*

- ***Meta-analysis of 8 clinical trials suggest some preventive effects of either oral or intravaginal probiotics (some delivered in yogurt), including women with HIV infection (one trial) in some but not all trials.***
- ***However, most of the relevant clinical trials had methodological problems such as small sample size, no control group, and included women without confirmed recurrent VVC.***

***J Antimicrobial Chemother* 2006;58:266-72.**

# *Vulvovaginal Candidiasis*
## *Prevention with Yogurt/Probiotics*

- *Small crossover trial with women with recurrent VVC found that daily ingestion of yogurt with L. acidophilus for 6 months reduced the mean number of infections and C. albicans colonization of the vagina and rectum when compared to 6 months with no yogurt consumption (0.38 vs. 2.54 [p = 0.001] and 0.84 vs. 3.23 [p = 0.001], respectively).[1]*
- *A RDBPCT in women (18-50 years) who were prescribed antibiotics for non-GU infections received an oral combination of L. rhamnosus and B. longum or oral placebo and/or a intravaginal pessary containing L. rhamnosus, L. delbrueckii, L. acidophilus, S. thermophilus or a placebo pessary (potencies or strain designators are not given) for 6 days during antibiotics and for 4 days after. The results fail to show a preventive effect for probiotics.[2]*


*1. Ann Intern Med 1992;116:353-7.*
*2. BMJ 2004;329:548-52.*

# *VVC in HIV-Positive Women*
## *Prevention with Probiotics*

- ***DBPCT with 164 HIV-positive women – randomized to one of three groups for 21 months:***
  - ***Intravaginal L. acidophilus (2 billion cfu; Gynatren) once per week***
  - ***Intravaginal clotrimazole (100 mg) once per week***
  - ***Intravaginal placebo once per week***
- ***The relative risk of developing VVC was 0.5 for the lactobacilli-treated group and 0.4 for the clotrimazole group compared to the control group. The median time to the first episode of VVC was longer for the lactobacilli group compared to placebo but did no reach statistical significance.***

***J Assoc Nurses AIDS 2001;12:51-7.***
***(reviewed in: Cochrane Database Systemic Rev 2011. Issue 8. Art No: CD008739)***

# *Vulvovaginal Candidiasis*
## *Adjunctive Use of Probiotics*

- ***RDBPCT with 55 women diagnosed with VVC. All were treated with a single dose of fluconazole (150 mg) and two oral capsules of either placebo or a combination of L. rhamnosus GR-1 and L. reuteri RC-14 ($1 \times 10^9$ of each organism per capsule) once daily for 28 days.***
- ***At 4 weeks, the probiotic group exhibited cure of VVC as determined by having no vaginal discharge, itching and/or burning, dyspareunia and/or dysuria and negative culture compared to the placebo group ($p < 0.05$). The probiotic treated group showed significantly less vaginal discharge (10.3% vs. 34.6%; $p = 0.03$) and lower presence of yeast detected by culture (10.3% vs. 38.5%; $p = 0.014$).***

***Letters Applied Microbiol 2009;48:269-74.***

# *Urinary Tract Infections*

- *Approximately 50-60% of women have a UTI during their lifetime. Recurrence of about 25-30% is seen in affected women.*
- *Most common in sexually active women 20-40 years old and postmenopausal women.[1]*
- *Vaginal colonization with E. coli is associated with depletion of vaginal $H_2O_2$-producing lactobacilli in women with recurrent UTI.[2]*


*1. Infect Dis Clin North Amer 2003;17:227-41.*
*2. J Infect Dis 1998;178:446-50.*

# *Urinary Tract Infections*
## *Prevention with Probiotics*

- *RDBPCT with 47 women (18-50 years) with > 3 episodes of symptoms in 12 mo received vaginal suppository containing either L. rhamnosus (≥ 7.5 x $10^8$ cfu) or placebo twice weekly for 26 wks. There was no difference in the incidence of symptomatic lower UTIs between both groups.[1]*
- *41 women (mean age 23 years) with symptoms of UTI plus bacteriuria were treated with antibiotics for 3 days and then randomized to vaginal suppositories (twice weekly for 2 weeks and then once at the end of the next two months) containing L. rhamnosus GR-1 and L. fermentum B-54 (≥ 1.6 x $10^9$ cfu) or sterilized skim milk. There was no significant difference in the rate of recurrence of lower UTI over 6 months – 21% in the probiotic group vs. 47% in the placebo group.[2]*


1. *Scand J Prim Health Care* 1994;12:239-43.
2. *Clin Ther* 1992;14:11-6.

# Prevention of Recurrent UTI
## *L. crispatus*

- *L. crispatus* CTV-05 proven *in vitro* to be highly adherent vaginal epithelial cells from premenopausal women with without a history of recurrent UTI.[1]
- RDBPCT - 100 women (median age 21 years) treated for acute UTI were randomized to receive either a vaginal capsule with *L. crispatus* CTV-05 ($10^8$ cfu/mL; Lactin-V) or placebo daily for 5 days after UTI treatment 7-10 days) and then once weekly for 10 weeks.
- In the probiotic group, the rate of culture-confirmed UTI was 15% compared to 27% for the placebo group (RR, O.5; 95% CI. 0.2-1.2).
- Women in the probiotic group that achieved a high level of *L. crispatus* colonization had a significant reduction in UTI recurrence compared to those who did not ($p < 0.01$).[2]


1. *J Urol* 2006;176:2050-4.
2. *CID* 2011;52:1212-7.

# *Gastrointestinal Tract Infections*

- ***Antibiotic-Associated Diarrhea***
- ***Clostridium difficile***
- ***Helicobacter pylori***
- ***Giardia lamblia***

# *Human Intestinal Microbiota*
## *Influence of Antibiotics*

- *Ciproflaxin caused rapid and profound change in gut microbiota in 3-4 days. By one week, there was a partial return to the initial state. However, by 10 months, the return was incomplete in some cases.*[1]
- *Clarithromycin and metronidazole cause a rapid and profound change in 1 week. Some recovered over time but, in some cases, perturbation of gut microbiota for up to 4 yrs post treatment.*[2]


1. *PNAS* 2011;108(suppl 1):4554-61.
2. *PLoS One* 2010;5:e9836.

# *Can Probiotics Prevent Disruption?*

- *Small DBPCT with 30 patients being treated for H. pylori. All subjects received 7 days of triple therapy (amoxycillin, metronidazole, lansoprazole) and were randomized to one of three groups:*
  - *Group 1 – Placebo from days 1 to 7*
  - *Group 2 – Placebo days 1 to 7 and probiotic* days 8 to 15*
  - *Group 3 – Probiotic days 1 to 15*
- *Stool samples were collected at days 1, 7, 12, 17, 27. The following was found:*
  - *Group 1 – facultative anaerobes were elevated at day 27*
  - *Group 2 – elevation from days 1 to 7 but decreased significantly between days 7 to 27*
  - *Group 3 – remained stable throughout*

**Lactobacillus acidophilus* CLT60 and CUL 21, *B. bifidum* CUL17 and Rhodia 2.5 x $10^{10}$ cfu/capsule*

*International Immunopharmacol 2005;5:1091-7.*

# *Antibiotic Associated Diarrhea (AAD)*

- ***The first report of antibiotic-associated diarrhea (AAD) was found in the *Bulletin of the Johns Hopkins Hospital* of 1893, where John Finney and Sir William Osler described the case of a young woman who died of a severe case of "diphtheric colitis" shortly after gastric surgery.***
- ***It was not until the mid-1900s, with the use of preoperative antibiotics, that AAD became a common medical problem.***

# *AAD, cont.*

- *The estimates of prevalence vary greatly - one source says 25% of adults and 11% of children (higher in very young children). One says it is infrequent in outpatient settings (< 0.1%).*
- *It is a benign, self-limited diarrhea following the use of antibiotics (usually 2-8 weeks after exposure) – most commonly those that have enterohepatic circulation. Most patients respond to supportive measures and discontinuation of antibiotics.*
- *Causes include:*
  - *Decrease in anaerobes reduces the metabolism of carbohydrates and a resultant osmotic diarrhea*
  - *Change in gut microflora results in overgrowth of potentially pathogenic organisms such C. difficile, Salmonella, C. perfringens type A, S. aureus, C. albicans.*

# *Clostridium difficile* Infection (CDI)

- *C. difficile* is a Gram-positive, spore-forming anaerobe thought to be the major cause of AAD in hospital settings. It is implicated in 25% of all AAD cases and 50-75% of all antibiotic-related colitis cases.
- The organism produces toxins that can cause severe colitis with or without the presence of pseudo-membranes.
- Although most episodes respond to metronidazole or vancomycin, recurrence of CDI after treatment occurs in up to 20% of all patients within 4 weeks and may be secondary to *C. difficile* spores that persist.

# *AAD*
## *Probiotics for Prevention*

| *Meta-Analyses* | *Studies* |
|---|---|
| • *J Pharmacol 2002;16:1461-7* | • *7* |
| • *BMJ 2002;324:1361-6* | • *9* |
| • *Aliment Pharmacol Ther 2005;22:365-72.* | • *5* |
| • *Lancet Infect Dis 2006;6:374-82.* | • *19* |
| • *Am J Gastroenterol 2006;101:812-22.* | • *25* |

***Probiotics reduce the incidence of AAD by about 50%***

# *AAD/CDI*

## *Probiotics for Prevention and Treatment*

- *Meta-analysis by McFarland reviewed 25 RCTs for prevention of AAD and 6 for treatment of CDI*
- *Probiotics reduced the relative risk of AAD (RR = 0.43, 95% CI 0.31-0.58; p < 0.001) and had significant efficacy for CDI (RR = 0.59, 95% CI 0.41-0.85; p = 0.005).*
- *For AAD, S. boulardii, L. rhamnosus GG, and some probiotic mixtures were found to be most effective. For CDI, only S. boulardii was found to be effective.**

**Note:* The author of the review is one of the PIs for two *S. boulardii* studies

*Am J Gastroenterol* 2006;101:812-22.

# *Pediatric AAD*
## *Probiotics for Prevention*

- *Meta-analysis includes 16 studies with 3,342 children.*
- *The incidence of AAD in the probiotic group was 9% compared to 18% in the control group but ITT analysis was non-significant overall*
- *An a priori analysis suggests that higher doses of probiotics (> 5 billion cfu/day) is more effective than lower doses (< 5 billion cfu/day) [p = 0.010]. In the high dose group, the NNT* to prevent one case of diarrhea is seven.*
- *Reviewers call for greater attention to drop-out rates and subjects lost to follow-up in future studies as well as greater standardization of organisms used.*

*Cochrane Database Syst Rev 2011;11:CD004827.*
*Number Needed to Treat

# *CDI*
## *Probiotics for Prevention and Treatment*

- *Other reviews have not been as positive:*
  - *Review limited to just S. boulardii reports on 4 studies – one showed a reduction of relapses; one showed a trend toward reduction in relapses; two looked at prevention of CDI in populations recently prescribed antibiotics but were under powered. "May be effective for secondary prevention."[1]*
  - *Cochrane Review finds no evidence to support the use of probiotics alone in the treatment of C. difficile colitis and insufficient evidence to recommend as an adjuvant to antibiotic therapy.[2]*


1. *Can J Gastroenterol* 2009;23:817-21.
2. *Cochrane Database Systematic Reviews* 2008;23:CD00461.

# *AAD/CDI*
## *Prevention with Probiotics*

- *RDBPCT with 135 hospital patients (mean age 74 years) taking antibiotics. Patients were randomized to receive either a 100 g (97 ml) drink containing L. casei DN-114 001 (1 x $10^8$ cfu/ml), S. thermophilus (1 x $10^8$ cfu/ml), L. bulgaricus (1 x $10^7$ cfu/ml) [Actimel, Danone] or a "sterile milkshake" as a placebo.*
- *There was a significant reduction in both the incidence of AAD (p = 0.007) and CDI (p = 0.001) in the probiotic group. After adjustment for covariates, the probiotic treatment reduced the odds of AAD by 75%.*
- *The study has been criticized for a very restrictive selection criteria (Honte à vous!).*

*BMJ 2007;335:80[Epub]*

# *AAD/CDAD*

## *Prevention with Probiotics*

- *RDBPCT with 225 adult inpatients were randomized to three treatment groups within 36 hrs of antibiotics and continued for 5 additional days after stopping antibiotics and were followed for an additional 21 days:*
  - *Group 1 – L. acidophilus CL1285, L. casei LBC80R* (100 billion cfu)*
  - *Group 2 – 50 billion cfu or the above combination*
  - *Group 3 - Placebo*
- *Group 1 had a lower incidence of AAD vs. Group 2 (15.5% vs. 28.2%, respectively) and both treatment groups compared to placebo (44.1%). In patients who had AAD, the incidence was shorter in Group 1 compared to Group 2 and placebo (2.8 days vs. 4.1 and 6.4, respectively).*
- *Group 1 had a lower incidence of CDAD compared to Group 2 and placebo (1.2% vs. 9.4% and 23.8%, respectively).*

**Bio K+ International, Laval, Quebec, Canada*

*Am J Gastroenterol 2010;105:1636-41.*

# *Helicobacter pylori*

- ***H. pylori* is a spiral-shaped, gram-negative bacteria that resides between the mucus layer and surface epithelial cells in the stomach or intestines. It colonizes when the mucosal integrity has been compromised.**
- **Estimated to infect 30-40% of the population in developed countries like the U.S.**
- **Colonization leads to ulcerations in the mucosal lining and causes peptic ulcer disease in up to 20% of infected individuals.**
- **Treatment consists of either triple or quadruple therapy that includes antimicrobials and acid suppressive drugs. Treatment fails in 10-35% of patients.**

# *H. pylori* Treatment

## *Probiotics – Reduction of side effects and improved eradication rates*

- *3 Meta-analysis with slightly different conclusions:*
  - *Probiotics may be beneficial in reducing adverse events and improving tolerability to treatment but do not affect eradication rates (4 studies).[1]*
  - *Review limited to Lactobacilli studies. Concludes that probiotics may improve eradication rates and reduce side effects such as diarrhea, bloating, and taste disturbance (8 studies).[2]*
  - *Three of 14 studies showed improved eradication rates. Similar conclusions to #2 above.*

*1. Ann Pharmacother 2011;45:960-6.*
*2. Helicobacter 2008;14:449-59.*
*3. Aliment Pharmacol 2007;25:155-68.*

# *H. pylori* Treatment
## Reduction of Side Effects with Probiotics

- *85 male and female patients with a diagnosis of H. pylori) infection - all were treated with a combination of rabeprazole, clarithromycin, and tinidazole for one week.*
- *During the 7-day treatment period and for 7 days after patients were randomized to additionally receive one of the following:*
  - *(1) a combination of L. acidophilus and B. lactis (approx. 10 billion organisms per day);*
  - *(2) Lactobacillus GG (approx. 12 billion organisms per day);*
  - *(3) S. boulardii (approx. 10 billion organisms per day);*
  - *(4) placebo.*

# *H. pylori* Treatment

## *Reduction of Side Effects with Probiotics, cont.*

- *The incidence of diarrhea was significantly lower in all three probiotic groups compared to the placebo group. The risk of diarrhea during week one for individuals treated with probiotics versus placebo was significantly lower as was the incidence of taste disturbance in all probiotic groups compared to placebo.*
- *There was no increased improvement in eradication in any probiotic group compared to placebo.*
- *Overall tolerability of treatment was significantly superior in all treatment groups compared to placebo.*

*Am J Gastroenterol 2002;97:2744-49.*

# *H. pylori* Treatment
## Improved Eradication with Probiotics

- *138 dyspeptic patients (mean age 47.7 years old) with an initial diagnosis of duodenal ulcers or gastritis were enrolled after one week of triple therapy (1 g amoxicillin, 500 mg clarithromycin, and 20 mg omeprazole b.i.d.) failed to eradicate H. pylori infection.*
- *Patients were randomized to receive either quadruple therapy (triple therapy plus 120 mg of bismuth subcitrate t.i.d.) either alone or following a 4-week pretreatment with yogurt containing an approximately equal mixture of Lactobacillus La5, B. lactis Bb12, L. bulgaricus, and S. thermophilus at a concentration of $\geq 10^9$ bacteria/ml. The amount of yogurt consumed was 200 ml b.i.d.*

# *H. pylori* Treatment

## Improved Eradication with Probiotics, cont.

- For patients in the yogurt-plus-quadruple therapy group infected with either antibiotic-sensitive or -resistant *H. pylori*, the excessive $\delta^{13}CO_2$/ml values of the $^{13}$C-urea breath test were significantly decreased after the 4-week ingestion of the probiotic-containing yogurt ($p < 0.0001$).
- The yogurt-plus-quadruple therapy group had a higher *H. pylori* eradication than did the quadruple therapy-only group (intention to treat analysis: 85% vs. 71.1%, respectively, $p < 0.05$; per-protocol analysis: 90.8% vs. 76.6%, $p < 0.05$).

*Am J Clin Nutr* 2006;83:864–9.

# *H. pylori* Treatment
## Probiotics – Negative Trial

- *62 adult H. pylori-positive patients with peptic ulcers or peptic ulcer scars and treated with triple therapy (esomeprazole, amoxicillin, clarithromycin) were randomized to no additional treatment or the addition of L. acidophilus (5 X $10^9$ cfu/capsule) – 3 capsules in the morning and 2 at night. Treatment was for 8 days.*
- *The main outcome was $^{13}C$ urea breath test (UBT).*
- *There was no difference in eradication rates between groups.*
- *Note that most earlier studies have used probiotics either before or, most commonly, after cessation of treatment.*

*Eur J Clin Microbiol Infect* 2011;30:555-9.

# *Anti-H. plyori* Probiotic Strain?

- *Spanish researchers have isolated a B. bifidum strain (CECT 7366) that has been shown to have potent anti-H. pylori activity*
- *In vitro inhibition has been found to be 82 – 95% and has been shown to be active in vivo in mice.*
- *Stay tuned (Manténgase en sintonía)*

*Appl Environ Microbiol* 2011;77:1335-43.

# *Giardia lamblia*
## *Improved Treatment Outcome with Probiotics*

- *65 adult patients with giardiasis were treated as follows: Group 1 (17 were symptomatic) was treated with 750 mg of metronidazole t.i.d. and 250 mg of encapsulated Saccharomyces boulardii b.i.d. for 10 days. Group 2 (15 were symptomatic) were treated with just metronidazole and placebo for 10 days.*
- *At the end of the 2nd week, G. lamblia cysts were detected in 6 cases (17.1%) in group 2 compared to no cases in group 1. The proportion of patients with clearance of microscopic findings after two weeks as 100% in group 1 compared to 82% in group 2 (p = 0.027).*

*Scand J Infect Dis 2006;38:479–81.*

# *Probiotic Safety*

- *Risk of translocation exists and probiotic-related sepsis has been reported in the literature. Proposed risk factors for probiotic sepsis (according to one source):*
- *Major risk factors*
  - *Immunocompromised, including a debilitated state or malignancy*
  - *Premature infants*
- *Minor risk factors*
  - *Central venous catheter*
  - *Impaired intestinal epithelial barrier, e.g., diarrheal illness, intestinal inflammation*
  - *Administration of probiotics by jejunostomy*
  - *Probiotics with properties of high mucosal adhesion or known pathogenicity*
  - *Cardiac valvular disease*

*Am J Clin Nutr 2006;83:1256-64.*

# *Probiotic Safety, cont.*

- *A group of Finnish researchers reviewed 89 cases of Lactobacillus bacteremia -- all of them adults (Clin Infect Dis 2004;38:62-9). The primary predisposing factors to bacteremia were immunosuppression, prior to prolonged hospitalization, and prior to surgical interventions. Detailed species characterization from blood cultures was available for 53% of these cases. Cases of bacteremia, as well as mortality, were usually associated with severe underlying comorbidities--82% of cases were classified as having either ultimately or rapidly fatal diseases.*
- *Bacteremia with S. boulardii has also been reported*

# *Probiotic Safety, cont.*

- *Despite concerns stated in previous slide, new data has found the following:*
  - *Probiotics actually decrease translocation of some pathogenic bacteria*
  - *Probiotics have now been extensively studied in very low birth weight infants with no safety issues*
- *Bottom line is probiotic supplements are safe for a broad spectrum of the population.*