Current and Future Applications of Probiotic Science

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Outline

- Current Status – Generally Accepted Uses and Safety
- Future Directions in Probiotic Research
- Clinical Studies - Issues
- Future – Role of the HMP
Current Status – Generally Accepted Uses and Safety
Generally Accepted Uses of Probiotics

● Where is the information coming from
  – Numerous published trials
  – Cochrane Reviews
  – Non-Cochrane Reviews and Meta-analyses

● Issues identified in Reviews
  – Cochrane
    • 12 published reviews – concerns about study quality, limiting conclusions
    • 13 files and protocols – not yet reported
  – Non-Cochrane Reviews and Meta-analyses
    • 17 published in 2009 and 2010 so far
    • Concerns about meta-analysis quality

● Issue often ignored in Reviews – which probiotic
Generally Accepted Uses of Probiotics

- Consensus Conferences
  - Many
  - Trend towards recommendations for use of specific probiotics at specified doses
  - Increasing recognition of gaps in knowledge
Generally Accepted Uses of Probiotics

● “A” recommendation (strong positive, well conducted, controlled studies)
  – Treatment of adult infectious diarrhea – S boulardii, LGG
  – Treatment of childhood infectious diarrhea – LGG, L reuterii
  – Prevention of AAD – S boulardii, LGG, L casei, L bulgaricus, S thermophilus
  – Pouchitis – VSL#3
  – Immune response – LGG, L acidophilus, L plantarum, B lactis, L johnsonii
  – Atopic eczema associated with cow’s milk allergy – LGG, B lactis

● “B” recommendation (some negative studies)
  – Prevention of diarrhea, treatment and prevention of CDAD, IBS

  Floch et al J Clin Gastro 2008; 42 (supp 2) S104
Generally Accepted Uses of Probiotics

● Safety concerns
  – risk of invasive disease, gene transfer, effect on immune system, metabolic effects

● What do we know about safety?
  – Safety data in published clinical trials - incomplete
  – Case reports and epidemiologic studies – likely incomplete
  – Phase I safety studies now appearing on clinicaltrials.gov
  – AHRQ/EPC study reviewing information on safety of Lactobacillus, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, *Bacillus*) – report 2010
Future Directions in Probiotic Research
Probiotic Trials 2005-2010 (Clinicaltrials.gov)

Purpose of Treatment:
- Normal
- Prevention
- Treatment

Count

Conditions
- Normal: 24
- Atopy and Allergy: 11
- Diarrhea: 19
- Other GI: 9
- Prematurity Respiratory: 7
- Other: 33

Conditions
- Normal
- Atopy and Allergy
- Diarrhea
- Other GI
- Prematurity Respiratory
- Other
Probiotic Trials 2005-2010 (Clinicaltrials.gov)

- Numerous ongoing trials
- Majority of trials continue to be conducted outside US
- Variety of probiotics being studied
  - Across the age spectrum
  - In an ever increasing range of diseases
  - Using a variety of routes of administration
- All IRB approved, regulatory oversight not clear
Clinical Studies - Issues
Clinical Trials Issues

- Questions about the quality of some previous probiotic research
  - Cochrane reviews – consequence - limitations to recommendations for use
  - FDA – consequence – need for Phase I safety studies in adults prior to proceeding to other populations
Clinical Trials Issues

● Probiotics as “therapy”
  – Biologic basis often not clear
  – Pre-clinical data – challenging and not always relevant
  – Safety profile – is “long history of use enough?”
  – Outcomes – often not clear

● Probiotics to “promote health”
  – What is “digestive health” etc? – need to know to study it

● Product Quality
  – FAO/WHO recommendations not always followed
Clinical Trials Issues

- Regulatory Status
  - Variably interpreted by investigators, IRBs, industry, lawyers? and possibly even FDA?
  - US - FDA – CBER
    - IND preparation burdensome for investigators and manufacturers
    - IND status – costs of research increase
  - Role of the standard drug/biologic development
    - Relevant to probiotics?
    - Small phase I safety studies in healthy subjects after numerous published studies in patient populations and widespread general use
Future – Role of the HMP
Probiotics and the HMP - Benefits

- Potential to understand the microbiota and how to safely manipulate it to prevent or treat disease

- Potential to understand the mechanisms of action of available probiotics to guide novel future probiotic strategies including personalized medicine

- Potential to develop novel outcomes, particularly needed where outcomes are difficult to define

- Potential to define biomarkers for safety and efficacy to improve efficiency of clinical trials
Probiotics and the HMP - Challenges

● Field is young
  – standardization and methods still being worked on
  – how to benefit from what is available now

● Need to know way more
  – not just what bugs are there
  – bug function, what generates pressure for function to change and how does function change
  – interaction with the mucosal (and systemic) immune system
Current and Future Applications of Probiotic Science - Conclusions

- Probiotics have a long history of use
  - Not as drugs or biologics
  - Numerous probiotics and reasons for use - biologic basis for use and evidence for use not always clear

- Numerous published and ongoing clinical trials with probiotics
  - Issues of trial quality and safety have been raised for some trials
  - Scientific basis for study of specific probiotic for specific indication not always clear

- Future
  - Understanding the microbiota – can/should/will this change probiotics as drugs/biologics and probiotics as foods/dietary supplements
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