Current Concepts in VAP: Stress Ulcer Prophylaxis & Probiotics

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Objectives

- **VAP**
  - The Old: Gastropulmonary route of infection
  - The New: Microbiome modification

- **Role of acid suppression**
  - Influence on VAP
  - Influence on other outcomes
  - REVISE Trial

- **Role of probiotics**
  - Influence on VAP
  - Influence on other outcomes
  - PROSPECT Trial
We are a walking ecosystem of bacteria and our health and normal development depends on them.

Bacteria, fungi, viruses
This collection of organisms is the microbiome.
What Is the Microbiome?

- Ecological community of commensal, symbiotic and pathogenic microorganisms .....in us or on us
- 10x more microbial than human cells
- **Microbiome** -- the collective **genomes** of the microorganisms
- **Microbiota** -- the **microorganisms**
The Human Microbiome Project

• NIH initiative launched in 2008 to identify and characterize microorganisms associated with both healthy and diseased humans
• 5 year project with $115 million budget
• Culture-independent methods (e.g., metagenomics)
  – Genetics of a single microbial community
  – Whole genome sequencing of individual bacterial species
The Human Microbiome

We can use a genetic “barcode” unique to each species of bacteria to define a community of bacteria.

Each type of bacteria has a distinct barcode or DNA signature.
The Human Microbiome

Measure the microbiome by sequencing these DNA barcodes in the bacteria - thousands or even millions at a time.
The Human Microbiome

The barcodes let us measure the diversity of bacteria present.

Classify them into groups

Make plots of the composition to compare
The `Modern Lifestyle` Is Influencing The Microbiome

- Humans are exposed to fewer microbes today
- Microbiome diversity correlated with better health
- Microbiome diversity is decreased today
  - Cesearean sections
  - Formulae feeding
  - Hygiene
  - Processed food
  - Indoor living
  - Antibiotics (animal, human)
  - Achlorhydria
Stress Ulcer Prophylaxis

• Stress ulcer bleeding used to be a common serious high mortality problem
• Acid suppression predisposes to intragastric gram negative organisms & aspiration pneumonia & altered GI microbiome
• Need to revisit the burden of illness for GI bleeding, VAP, \textit{C difficile}
• The NNP might have increased
• The NNH might have decreased
• The cost per bleed averted might have increased
Stress Ulcer Prophylaxis: Do the benefits outweigh the risk?

- Bleeding prevention
- Pneumonia CDI
Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients

- 1,034 patients in 97 ICUs in 11 countries
- Clinically important GI bleeding 2.6% (1.6-3.7)
- Independent risk factors
  - 3 or more coexisting diseases
  - Liver disease
  - Renal replacement therapy
  - High SOFA
Clinically important bleeding (favouring PPI-H$_2$RA)

- RR 0.41 (0.31-0.53), I$^2$ = 48%
  (22% of required information size)

Pneumonia

- RR 1.16 (0.84-1.58), I$^2$ = 19%
  (12% of required information size)

*Clostridium difficile*

- no results
Clinically important bleeding favouring PPIs

- RR 0.36 (0.19-0.68), $I^2 = 0$

Pneumonia

- RR 1.06 (0.73-1.52), $I^2 = 0$

Clostridium difficile

- no results
REVI SE

Re-Evaluating the Inhibition of Stress Erosions: Gastrointestinal Bleeding Prophylaxis In ICU
Research Question: Pilot RCT

In mechanically ventilated critically ill patients, is it feasible to perform a large RCT to investigate the impact of pantoprazole compared to placebo on clinically important bleeding in terms of

1. Informed consent rate (mixed model)
2. Recruitment rate
3. Protocol adherence
What are Probiotics?

Commercially available microorganisms which, when ingested as individual strains or in combinations, offer potential health benefits to the host

World Health Organization
Proposed Mechanisms of Benefit

- Re-inoculate of indigenous microflora
- Re-establish microbiome diversity
- Inhibit pathogen adhesion & invasion
- Improve gut mucosal barrier function
- Reduce bacterial translocation
- Toll-like receptor-mediated up-regulated immunity
- In trauma RCT (N=52, Tan et al Crit Care 2011)
  - faster increase in T helper 1 cytokines IL-12 p70
  - improved cellular immunity & macrophage function
In any further work that is undertaken, it may be worth concentrating on specific groups of patients, e.g. trauma patients. Even within these studies there is considerable heterogeneity with regard to probiotic species used and dosage, route and timing of administration. In future research careful consideration should be given to these factors, as well as greater measures taken to better assess the safety of probiotics.
Determining the Ideal Strategy for Ventilator-associated Pneumonia Prevention
Cost–Benefit Analysis

Westyn Branch-Elliman¹, Sharon B. Wright²,³, and Michael D. Howell⁴,⁵

Figure Legend
ETT = Endotracheal tube
OD = Oral decontamination
DD = Digestive decontamination
● = Decision node
▲ = Terminal node
Strategy with best cost-benefit ratio:
+ Suction ETT
+ IHI Bundle with oral care
+ Probiotics

2014 Compendium of Strategies to Prevent Healthcare Associated Infections in Acute Care Hospitals
PROSPECT

PRObiotics to prevent Severe Pneumonia and Endotracheal Colonization Trial
Research Question: Pilot RCT

Is it feasible to perform a large RCT in mechanically ventilated critically ill patients to evaluate whether oral *L. rhamnosus* GG prevents VAP, based on

- timely recruitment
- maximal protocol adherence
- minimal contamination
- an acceptable VAP rate?
Coenrolment: PROSPECT & REVISE

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<td><strong>Intervention</strong></td>
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<td><strong>Primary Outcome</strong></td>
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<td>Clin imp upper GI bleeding</td>
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<td><strong>Secondary Outcomes</strong></td>
<td>Infections including C diff</td>
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Coenrolment: PROSPECT & REVISE

- Probiotics may lower VAP & C difficile
- PPIs may raise VAP and C difficile

- We’re recording PPIs in PROSPECT
- We’re recording probiotics in REVISE
Conclusions

• The microbiome in critical illness is poorly understood
• 2 low-tech, low-cost, widely available interventions influence the microbiome of the respiratory tract and gut differentially
  – probiotics
  – stress ulcer prophylaxis
• Understanding their impact on nosocomial infections is a clinical & research priority
100 Trillion Friends you didn't know you had
Thank you for the invitation!
Research Question

Is a large RCT in mechanically ventilated critically ill patients to evaluate whether oral *L. rhamnosus* GG prevents VAP feasible, based on

1) Timely recruitment: if $\geq 2$ pts/wk in 1 yr

2) Maximal protocol adherence: if $\geq 90\%$ of prescribed doses are actually administered

3) Minimal contamination: if $\leq 5\%$ of patients receive a dose of open-label probiotics

4) Acceptable VAP rates: if $\sim 10\%$
Coenrolment: PROSPECT & REVISE

• **Probiotics** may lower VAP and *C. difficile* risk
• **PPIs** may raise VAP and *C. difficile* risk

• We’re recording PPIs in PROSPECT
• We’re recording probiotics in REVISE

• Probiotic use may increase; practice varies globally
• PPI use may decrease; practice varies globally