Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

The use of probiotics for patients in hospitals
A benefit and risk assessment

Opinion of the Steering Committee of the Norwegian Scientific Committee for Food Safety

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The use of probiotics for patients in hospital; a benefit risk assessment

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Persons working for VKM, either as appointed members of the Committee or as *ad hoc* experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

Acknowledgements

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II. Terminology and definitions

AIDS: Acquired Immune Deficiency Syndrome
AAD: Antibiotic Associated Diarrhoea
CDAD: *Clostridium difficile* Associated Disease
HUS: Haemolytic-uremic syndrome
IBD: Inflammatory bowel disease
IBS: Irritable bowel syndrome
LGG: *Lactobacillus rhamnosus* GG
NAFLD: Non-alcoholic fatty liver disease
NEC: Necrotizing enterocolitis
MIC: Minimum Inhibitory Concentration
SIBO: Small intestinal bacterial overgrowth

Mobile genetic element: General terms for any genetic unit that can insert into a chromosome, exit, and relocate; includes insertion sequences, transposons, some bacteriophages, and controlling elements. A region of the genome flanked by inverted repeats, a copy of which can be inserted at another place; also called a transposon or a jumping gene. (http://www.biochem.northwestern.edu/holmgren/Glossary/Definitions/Def-T/transposable_genetic_eleme.html).

Prebiotic: A prebiotic is a non-viable food component that confers a health benefit by modulation of the gut microbiota (FAO 2007)

Probiotic: Live microorganisms which, when administered in adequate doses, confer a health benefit on the host (FAO 2001)

Synbiotic: A product that contains both probiotics and prebiotics (Schrezenmeir & de Vrese 2001)

III.i. Summary

Because of a long history of the safety of lactic acid bacteria and bifidobacteria, many probiotic microorganisms are granted GRAS (generally regarded as safe) and QPS (Qualified Presumption of Safety) status in the United States and in European Union, respectively.

The present opinion is related to the general use of products supplemented with probiotic microorganisms for the seriously ill and hospitalized patients, and possible hazards connected with this practice. The Norwegian Food Safety Authority received an enquiry from Stavanger University Hospital (SUH) regarding the use of probiotics for hospital patients. The article '*Probiotic use in clinical practice: what are the risks?*' (Boyle *et al.*, 2006) and the previous risk assessments by the Scientific Committee for Food Safety (VKM) (www.vkm.no) concerning the use of LGG in infant formula food prompted the need for a further assessment of possible benefits and risks related to the use of probiotics for hospital patients. VKM was therefore asked by The Norwegian Food Safety Authority to assess benefits and risks concerning the use of probiotics or products containing probiotics, for specific groups of hospital patients. In response, the VKM Panel on biological hazards and the VKM Panel on nutrition, dietetic products, novel food and allergy appointed an *ad hoc* Working Group of experts which was given the mandate to provide the necessary background for a risk assessment. Focus has not only been on critically ill hospital patients, but also on critically ill individuals who are not being cared for in hospital, such as cancer patients and other immunocompromised individuals. The assessment has been evaluated and approved by the Scientific Steering Committee of VKM.

This risk assessment is based on reviews of published literature, mainly from the last two to three years. The following main topics have been reviewed: bacterial translocation from the gut and infectious disease; virulence factors including toxicity; metabolic functions including host storage, platelet aggregation, deconjugation of bile acids, and degradation of mucin. Furthermore, resistance to antimicrobials, with emphasis on the genes involved, has been studied.

Clinical implications are emphasized in the assessment. Several reports demonstrate possible beneficial health effects of probiotic supplementation, especially for the treatment of rotavirus-associated diarrhoea. Most studies focus on possible beneficial short-term effects and not on long-term safety.
Studies concerning probiotic supplementation in hospital patients suffering from acute pancreatitis, antibiotic-associated diarrhoea (AAD) including *Clostridium difficile* infection (CDAD) and non alcoholic fatty liver disease (NAFLD) are reviewed. Furthermore, supplementation with probiotic bacteria in critically ill children, i.e. children in intensive care is discussed. Finally, the use of probiotics in patients with diarrhoea, *Helicobacter pylori* infection and inflammatory bowel disease is mentioned, as well as in patients with AIDS, urogenital infections, and small intestinal bacterial overgrowth.
There is no evidence of beneficial effect by supplement of probiotics on critically ill patients with diseases mentioned above. Particular attention has been paid to a large study carried out in the Netherlands which investigated the use of synbiotics in patients with acute pancreatitis (PROPATRIA). In that study it was concluded that in patients with predicted severe acute pancreatitis, probiotic prophylaxis with that particular combination of probiotic strains did not reduce the risk of infectious complications but was in fact associated with an increased risk of mortality.

Although some studies indicate a prophylactic effect of probiotic supplementation on AAD and CDAD, there is a general agreement that probiotics are contraindicated in critically ill patients with these diseases.
There are similarities in some acquired resistance genes between probiotic microorganisms and bacteria of human origin, which may suggest the spread of resistance genes between commensal microorganisms in the complex ecosystem. Intake of probiotic microorganisms that bear mobile antimicrobial resistance genes may increase the risk of the transfer of such genes to the resident microbiota and thereby increase the problem of treating nosocomial infections.

The Norwegian Scientific Committee for Food Safety concludes that although some beneficial effects have been reported in some patient groups, the adverse effects that have been observed are well documented, thus indicating that probiotic bacteria should not be consumed by critically ill individuals.

III.ii. Sammendrag

På grunn av en lang historie om sikkerhet ved bruk av laktobaciller og bifidobakterier er mange probiotiske bakterier gitt status som GRAS (generally regarded as safe) og QPS (Qualified Presumption of Safety) i henholdsvis USA og EU.

Mattilsynet har mottatt en forespørsel fra Stavanger Universitetssykehus (SUH) vedrørende bruk av probiotika blant sykehuspasienter. Artikkelen '*Probiotic use in clinical practice: what are the risks?*' (Boyle *et al.*, 2006) og tidligere risikovurderinger fra Vitenskapskomiteen for mattrygghet (VKM) (www.vkm.no) om tilsetning av LGG i morsmelkerstatning viser at det er behov for en ytterligere vurdering av mulige positive og negative helseeffekter knyttet til bruk av probiotika blant sykehuspasienter. VKM har nedsatt en *ad hoc*-gruppe med eksperter på dette fagområdet. *Ad hoc*-gruppens mandat har vært å utarbeide et utkast til en risikovurdering om bruk av probiotika eller produkter som inneholder probiotika blant spesifikke grupper sykehuspasienter. *Ad hoc*-gruppen har i tillegg vurdert bruk av probiotika blant kritisk syke som får pleie utenfor sykehus, for eksempel kreftpasienter og andre individer som er immunosupressive. Risikovurderingen fra ad hoc-gruppen er diskutert i faggruppen for hygiene og smittestoffer og faggruppen for ernæring (human), dietetiske produkter, ny mat og allergi, og er evaluert og godkjent i VKMs hovedkomité.

Denne risikovurderingen er basert på gjennomgang av publiserte studier - hovedsaklig fra de siste 2-3 årene. Følgende hovedemner er belyst: bakteriell translokasjon fra tarm og infeksjonssykdommer, virulensfaktorer (herunder toksikologiske), bakterielle metabolitter (effekt på vert), plateaggregering, dekonjugering av gallesyrer, degradering av mucin og antibiotikaresistens med vekt på genetikk.

Flere studier viser mulig gunstig effekt av probiotika, særlig ved rotavirus-assosiert diaré. De fleste publiserte studiene som omhandler probiotika undersøker mulige positive (kortvarige) helseeffekter, og er ikke designet for å granske sikkerhet og eventuelle uønskede effekter ved langtidsbruk.

I risikovurderingen er det lagt vekt på probiotikatilførsel hos pasientgrupper med alvorlige kliniske komplikasjoner som akutt pankreatitt, antibiotika-assosiert diaré (AAD), *Clostridium difficile*-infeksjon (CDAD) og non-alcoholic-fatty-liver-disease (NAFLD), også pasienter med diaré, *Helicobacter pylori*infeksjon og inflammatorisk tarmsykdom (IBD), urogenitale infeksjoner, og pasienter med økt bakteriell vekst i tynntarmen (SIBO) samt bruk av probiotika blant kritisk syke barn er vurdert.

Det er ikke funnet bevis for gunstig effekt av tilførsel av probiotika til alvorlig syke pasienter med sykdommer som er nevnt over.

En omfattende studie fra Nederland som har sett på bruk av synbiotika blant pasienter med akutt pankreatitt (PROPATRIA) er særlig vektlagt i risikovurderingen. I den nederlandske studien ble det konkludert med at probiotisk profylakse ikke reduserte risikoen for komplikasjoner, men faktisk var assosiert med økt risiko for dødelig utgang hos pasienter med alvorlig akutt pankreatitt.

Selv om noen studier indikerer en profylaktisk effekt av probiotika når det gjelder AAD og CDAD, er det en generell enighet at probiotika er kontraindisert hos kritisk syke pasienter med disse sykdommene.

Det er likheter i enkelte ervervede resistensgener i probiotiske bakterier og humane bakterier, noe som kan indikere at spredning av resistensgener mellom kommensale bakterier i et komplekst økosystem kan forekomme. Inntak av probiotiske mikroorganismer med mobile antimikrobielle resistensgener kan teoretisk sett øke risikoen for overføring av slike gener til mikrofloraen og dermed gi problemer ved behandling av nosokomiale infeksjoner.

VKM konkluderer med at selv om det er rapportert enkelte positive helseeffekter for noen pasientgrupper, så er de negative helseeffektene ved tilførsel av probiotika som har blitt observert, er nå godt dokumentert. Probiotika bør derfor ikke gis til kritisk syke pasienter.

IV. Background

Because of a long history of the safety of lactic acid bacteria and bifidobacteria, many probiotic microorganisms are granted GRAS (generally regarded as safe) status in the United States (Liong 2008) when given to healthy individuals. However, during the last 2-3 years a number of scientific papers have been critical regarding use of probotics in clinically ill patients.

The Norwegian Food Safety Authority received a communication from Stavanger University Hospital (SUH) regarding the use of probiotics for hospital patients. The article '*Probiotic use in clinical practice: what are the risks?*' (Boyle *et al.*, 2006) and also the risk assessment from the Norwegian Scientific Committee for Food Safety (VKM) on the use of LGG in infant formula and baby foods for healthy babies and infants (www.vkm.no), prompted SUH to request a general assessment of the use of probiotics for hospital patients, both adults and children.

SUH noted that probiotics, such as for example "Biola", a dairy product, are often given to patients with diarrhoea, and also as prophylaxis for patients on antimicrobial therapy. The amount given is variable; the usual amount for adults can be 100 ml taken between 1 and 4 times daily during treatment with antimicrobials.

In October 2007, The Norwegian Food Safety Authority (Mattilsynet) asked the VKM Panel on biological hazards and the VKM Panel on nutrition, dietetic products, novel food and allergy to address this issue (2007/55034/gyomj/1004002). In response, the VKM Panel on biological hazards and the VKM Panel on nutrition, dietetic products, novel food and allergy appointed an *ad hoc* Working Group of experts with the mandate to provide an assessment of benefits and risks concerning the use of probiotics, or products containing probiotics, for specific groups of hospital patients. As these same patient groups may also be treated outside a hospital setting, it is pointed out that the conclusions also apply to patients outside the hospital.

The mandate states that focus should be on strains of probiotic bacteria already found in products on the Norwegian market. The assessment, however, also includes other probiotic bacteria in our assessment as new probiotic food products, since strains at present novel to the Norwegian market, are constantly emerging. The assessment, however, also includes other probiotic bacteria in new probiotic food products, since strains which are presently novel to the Norwegian market are constantly emerging.

V. Terms of reference[1]

The Norwegian Food Safety Authority has requested VKM to address the following questions:

1) What benefits can be derived from the use of probiotics, or products containing probiotics, by different groups of hospital patients? For example:
   - children with serious or chronic illnesses,
   - pregnant women (e.g. those with hyperemesis, with enteral nutrition delivered directly to the small intestine),
   - patients with chronic illnesses, particularly those with intestinal diseases,
   - the seriously ill (e.g. bone marrow transplant patients),
   - immuno-compromised patients,
   - recently-operated patients.

2) Are there any contraindications for the use of probiotics, or products containing probiotics, for different groups of hospital patients? For example:

1

Mandat

I samarbeid med VKM har det blitt utarbeidet et mandat for gruppen som skal vurdere problemstillingen.

Mattilsynet ber VKM om å vurdere følgende spørsmål:

1. Hvilken nytte kan sykehuspasienter ha av å bruke probiotika eller produkter inneholdende probiotika, for eksempelvis;
   - barn med alvorlig eller kronisk sykdom
   - gravide - f.eks. hyperemesis pasienter som sondes direkte til tynntarm
   - pasienter med kronisk sykdom spesielt de med tarmsykdommer
   - alvorlig syke - eks. beinmargstransplanterte
   - pasienter med redusert immunforsvar
   - nyopererte

2. Er det noen kontraindikasjoner ved bruk av probiotika eller produkter inneholdende probiotika, til sykehuspasienter, for eksempelvis;
   - barn med alvorlig eller kronisk sykdom
   - gravide – f.eks. hyperemesis pasienter som sondes direkte til tynntarm
   - pasienter med kronisk sykdom spesielt de med tarmsykdommer
   - alvorlig syke – f.eks. beinmargstransplanterte
   - pasienter med redusert immunforsvar
   - nyopererte

3. Er det fare for at bruken av probiotika kan føre til en økt antimikrobiell resistensutvikling? Kan dette for eksempelvis være årsak til, eller føre til en økning i antall sykehusinfeksjoner?

Gruppen bes å ha et hovedfokus på de probiotika som eksisterer på det norske markedet i dag.

Lactobacillus Rhamnosus GG (LGG) – Biola
Bifidobacterium lactis BL™ - Danone/Activia
Lactobacillus casei F 19 – Flerkornsgrøt med probiotika (barnemat)
Lactobacillus acidophiluskultur LA5 – Biola, Cultura, Probiotic Drink
Bifidobacterium animalis ssp. lactis BB12 – Biola, Cultura, Probiotic Drink, Proviact

Det er vurdert at probiotiske kosttilskudd i liten grad gis til sykehuspasienter. Eventuelle andre bakteriestammer, enn de som er nevnt ovenfor, som brukes i denne typen produkter er derfor ikke inkludert i mandatet.

- children with serious or chronic illnesses
- pregnant women (e.g. those with hyperemesis, with enteral nutrition delivered directly to the small intestine),
- patients with chronic illnesses, particularly those with intestinal diseases,
- the seriously ill (e.g. bone marrow transplant patients),
- immuno-compromised patients,
- recently-operated patients.

3) Is there any risk that the use of probiotics can result in an increased development in resistance to antimicrobials? For example, can the use of probiotics be a reason for, or result in, an increase in the number of intractable nosocomial infections?

It is requested that the main focus should be on those probiotics currently available on the Norwegian market:

Lactobacillus rhamnosus GG (LGG) – Biola
Bifidobacterium lactis BL™ – Danone/Activia
Lactobacillus casei F19 – Multigrain porridge with probiotics (baby food)
Lactobacillus acidophilus LA5 – Biola, Cultura, Probiotic Drink
Bifidobacterium animalis ssp. *lactis BB12* – Biola, Cultura, Probiotic Drink, Proviact

It is considered that capsules containing probiotics are not given to hospital patients in significant amounts. Therefore, bacterial types, other than those listed above, which may be used in that type of product, are not included in the mandate.

VI. Hazard identification

Hazard identification is implicit in the terms of reference.

VII. Hazard characterization

For general information regarding characterization of hazards in probiotic microorganisms, see our previous reports on the use of LGG as an ingredient in baby food and infants formula (www.vkm.no) and the following publications: (FAO 2001; Scientific Committee on Food.European Commission.Health and Consumer Protection Directorate-General. 2004; Wassenaar & Klein 2008; Scarpellini *et al.*, 2008).

VII.i. Characteristics of probiotics

VII.i.i. The fate of probiotics in the intestine

The effect of probiotics depends upon their ability to survive passage through the stomach and duodenum and their ability to be transiently present in, or to “colonize”, the intestinal lumen in intestinal compartments (virtually mostly unknown) for an undefined time period. When present, they may be able to interact with both the host and the indigenous microbiota. In both types of interactions, any potential health benefit will depend on the functional profile of the probiotics and on those compartments in which they are present.
In the human host, interactions can be on a physiological, biochemical and/or immunological level. A few, but not all, probiotic strains can reduce intestinal transit time, improve the quality of migrating motor complexes (regularly occurring muscular contractions in the small intestine) (Husebye *et al.*, 2001), and temporarily increase the rate of mitosis in enterocytes (Banasaz *et al.*, 2002).

Some, but not all, probiotic strains can deconjugate bile acids and other compounds present in bile (bilirubin, steroids, xenobiotics) (example: the active components in contraceptive drugs are conjugated in the liver and have an enterohepatic circulation). It is often claimed that probiotics can "normalize" the indigenous flora, by mechanisms not yet satisfactorily described. Indeed, a definition of a "normal" microbiota does not exist. It has to be kept in mind that probiotics are live microbes that, in order to exert any effect, have to be metabolically active. It follows that their metabolism may have a beneficial, neutral or deleterious effect on the microbes within the host microbiota.

VII.i.ii. Translocation and infectious disease

The translocation of probiotic microorganisms in immunocompromised patients has been documented in several papers. The review article by (Isakow *et al.*, 2007) discussed the occurrence of probiotic microorganisms in numerous nosocomial infections:

1- **Endocarditis**; This may be due to the ability of the probiotic microorganisms to aggregate platelets and/or bind to the extracellular matrix of endothelial cells. (Harty *et al.*, 1993; Harty *et al.*, 1994; Salvana & Frank 2006). (See also - VII.v.i)

2- **Bacteraemia**; over a 5 year period, 45 patients at a clinic in USA developed bacteraemia from which *Lactobacillus* was isolated (Husni *et al.*, 1997). How many of these patients had underlying co-morbidities such as cancer, recent abdominal surgery, diabetes mellitus or immunosuppression, and in addition received probiotics was not reported. The bacteraemia was polymicrobial in 27 of 45 cases. Thirty one of these 45 patients died, but only one death was considered to be attributable to *Lactobacillus* bacteraemia. (Ledoux *et al.*, 2006) reported one case of bacteraemia and septic pulmonary emboli with *Lactobacillus acidophilus* in a patient with AIDS and Hodgkins, who had taken probiotics containing this species of bacteria.

3- **Pneumonia**; *Lactobacillus* pneumonia has been reported in immunosuppressed patients with AIDS (Abgrall *et al.*, 1997), after lung transplantation (Jones *et al.*, 1994), and after liver transplantation (Patel *et al.*, 1994). However, it is not clear that the source of the *Lactobacillus* isolates was as a consequence of probiotic consumption. *Lactobacillus* ventilator-associated pneumonia has also been also reported in a critically ill trauma patient (Woods *et al.*, 2002).

4- **Possible septicaemia and isolation from blood culture**
Saccharomyces cerevisiae fungemia has been reported in a critical care population receiving *Saccharomyces boulardii*-containing probiotics. There are now more than 50 cases reported in the literature and more than half of the patients were consuming probiotic products (Lherm *et al.*, 2002; Munoz *et al.*, 2005).
In a study performed by (Lolis *et al.*, 2008), the authors conclude that the incidence of *S. boulardii* fungemia is probably underestimated in critically ill patients.

Eighty-five *Lactobacillus* isolates from blood cultures in Finland were identified to species level and tested for antimicrobial susceptibility (Salminen *et al.*, 2004; Salminen *et al.*, 2006). The species among those isolates tested were: *L. rhamnosus* (n = 46), *L. fermentum* (n =12), and *L. casei* (n = 12). Of 46 *L. rhamnosus* isolates, 22 were identified as LGG type by pulsed-field gel electrophoresis. Most clinical *Lactobacillus* isolates demonstrated low MICs of imepenem, pieracillin-tazobactam, erthytromycin and clindamycin, but they had variable susceptibility to penicillin and cephalosporins.

5- **Liver abscess**

Although it is extremely rare, liver abscesses can be associated with *L. acidophilus*. There is reference to a single case in an immunocompromised (due to steroid treatment) patient with Crohn's disease (Cukovic-Cavka *et al.,* 2006).

VII.ii. Virulence factors

Toxicity

Concerning the probiotic strains under evaluation in this report, the *ad hoc* group found no reports of production of specific toxins, deleterious to the host body, by these strains.

VII.iii. Aspects of probiotic metabolic functions

VII.iii.i. Host storage of microbial products

For more than 1 ½ centuries, microorganisms have been assumed to play a role in development of atheromatosis (Virchow 1856). Developments in molecular technology have made it possible to search for the presence of specific microbial cell components in atheromatoseous plaques as well as in other chronic lesions (rheumatoid arthritis etc), and components from several different species of microorganisms have been found. However, the aetiopathological role(s) of these findings is still under debate, and components originating from probiotic strains have not yet been found. To the best of our knowledge, the strains of probiotic bacteria available on the Norwegian market have not been included in any such studies.

VII.iii.ii *Platelet aggregation*

a. Endocarditis. Another area of concern is whether, and to what extent, probiotics may contribute to development of infectious endocarditis. Platelet aggregation contributes to the pathogenesis of infectious endocarditis and some microorganisms (e.g. some streptococci) (Plummer & Douglas 2006) may increase platelet aggregation. So far however, very few studies have been found in which probiotic strains were investigated for their platelet aggregation properties (Harty *et al.,* 1993; Harty *et al.,* 1994; Zhou *et al.,* 2005). As stated by (Harty *et al.,* 1994), this "platelet-aggregating property is not uncommon in the genus". However, the *ad hoc* group found no information on this aspect for the probiotic strains on the Norwegian market
b. Haemolytic-uremic syndrome (HUS) is the most common cause of acute renal failure in children under 3 years of age. It may also occur in adults. In most countries, diarrhoea-associated HUS accounts for around 90 % of all HUS (Blahova 2004) and this is also the case in Norway. A major pathogenic trait is platelet aggregation (Blahova 2004; Franchini *et al.,* 2006). Whether, and to what extent, the presence of other microbes (including probiotics) with platelet aggregation properties may aggravate HUS has not been investigated. However, as long as this possibility exists, there is a need for further investigations into the effects of those probiotic strains on the market.

VII.iii.iii. *Deconjugation*

Conjugation is a mechanism by which the human organism regulates the metabolism, function, excretion and re-circulation of many endogenous and exogenous compounds, including many drugs. Most conjugating processes take place in the liver. The four molecules most often used for conjugation are: glycine, taurine, glucuronic acid and sulphate. Many of the conjugated compounds are excreted by the bile into the small intestine and many of them undergo an entero-hepatic circulation.

If deconjugating enzymes are present in the intestine, the conjugates might be deconjugated, resulting in marked alterations in physiochemical properties. These alterations might have physiological, as well as pathophysiological, consequences.

Intestinal deconjugation of glycin and taurine conjugates is always microbial; the same holds true for more than 99 % of the deconjugation of glucuronic acid conjugates and most probably, for a substantial part of sulphate conjugates. Under physiological conditions, only a minor part of microbial deconjugation takes part in the small intestine. If increased deconjugation takes place, some pathophysiological conditions may occur (decreased bile acid re-circulation, steatorrhoeae, reduced efficacy of contraceptive drugs and of other drugs with an entero-hepatic circulationetc etc).

Regarding lactobacilli and bifidobacteria, it has long been known that strains of both groups are able to deconjugate either glycine, taurine or both types of conjugates (Midtvedt 1974). In general, deconjugated bile acids are generally moreinhibitory to other bacteria than conjugated bile acids (Dunne et al 2001).
Experimental data indicate that some bile acid derivatives may influence the production of cholecystochin, which in turn may influence development of acute pancreatitis in an obstruction model (Barrett et al 2006, Samuel et al 2004). These observations might be of some value in explaining the aggravation of acute pancreatitis following jejunal administration of some probiotics.

Many strains produce beta-glucuronidases, enzymes capable of splitting glucuronic acid conjugates. Information on whether, and to what extent, probiotic strains contain enzymes capable of splitting sulphate conjugates, is unavailable. At present, the *ad hoc* group has no information on the ability of the probiotic strains on the Norwegian market to split the types of bile conjugates mentioned above. It has been argued that since the probiotics are given 1-2 times a day, the microbes are present in the small intestine for a short period of time. However, studies in patients with ileostomy clearly show that orally given probiotics do not reach the stomi in a single bolus, but with a substantial “tail”. It therefore seems reasonable to assume that they are biochemically active for a substantial time period

In summary, deconjugation is an important intestinal microbial function, especially if it takes place in the small intestine. Under physiological conditions, an increased deconjugation may have minor consequences for the host. However, in some clinical conditions, such as in particular critically ill patients, any interference with compounds excreted by the bile and/or with an entero-hepatic circulation, de-conjugation may have major consequences for the host. Under such conditions, the possible pathophysiological consequences have to be evaluated, strain by strain, endogenous conjugate by endogenous conjugate, and drug by drug, before a probiotic is given.

VII.iii.iv. ***Degradation of mucin***

A large amount of mucin is produced in the gastrointestinal tract by Goblet cells and enterocytes. The production of mucin parallels postnatal bacterial colonization and a wide array of bioactive factors that are able to stimulate mucin production have been described in the scientific literature. Mucin has many functions, and the most

important one might be to act as a first line of defence for the underlying cells (Franchini *et al.,* 2006). Several antimicrobial peptides (defensins) are produced along the whole gastrointestinal tract and these peptides are retained by the surface-overlaying mucin, thereby providing a combined physical and antibacterial barrier against bacterial attachment and translocation (Meyer-Hoffert *et al.,* 2008).
Under physiological conditions, gastrointestinal mucin is broken down by the indigenous microbiota, leaving little mucin to be excreted in faeces. It has been claimed, although never satisfactorily shown, that probiotics may regulate the balance between production and degradation of mucin. From the above, it can be summarized that decreased production or increased degradation of mucin may have pathophysiological consequences, especially in critically ill patients. Administration of probiotics with these functions should be avoided in these patients. Whether, and to what extent, probiotic strains on the Norwegian market are able to influence mucin metabolism is unknown.

VII.iv. Antimicrobial resistance

Probiotic strains belonging to *Lactobacillus* and *Bifidobacterium* may be resistant or susceptible to clinically-relevant antimicrobials. All *Lactobacillus* strains, but not all *Bifidobacterium,* are intrinsically resistant against vancomycin. Additionally**,** it has recently been demonstrated that the *vanA* gene from enterococci may be transferred to a commercial strain of *Lactobacillus acidophilus* (Mater *et al.,* 2005; Mater *et al.,* 2008). The transformation occurred not only *in vitro*, but also *in vivo* in the gut of mice with no antimicrobial pressure. The transconjugants arose at relatively high frequencies and were able to persist in the digestive environment. These studies confirm that horizontal gene transfer of antimicrobial resistance genes may occur in the gastrointestinal tract of animals and humans. This is of particular concern in hospital patients.
So far, multi-resistance seems to be uncommon among LAB and bifidobacteria species but, in particular, tetracycline and erythromycin resistance determinants may be isolated (Ammor *et al.*, 2007). There is a similarity between many of these gene determinants in bacteria of human origin and LAB / bifidobacteria, which confirms that the spread of resistance genes between commensal microorganisms in the complex ecosystem does occur. In the past, many of the antimicrobial resistance genes in probiotic microorganisms such as *Lactobacillus* and *Bifidobacterium* strains were found to be located on the chromosome. Recently several antimicrobial resistant determinants in these microorganisms have been found to be located on plasmids (Florez *et al.,* 2006) and other mobile DNA-elements (Ammor *et al.,* 2007; Alvarez-Martin *et al.,* 2007; Florez *et al.,* 2008; Ammor *et al.,* 2008a; Ammor *et al.,* 2008b). It is generally believed that if antimicrobial resistant genes are carried on mobile genetic elements (e.g. plasmid, transposons) then the potential exists for transfer from probiotic microorganisms to other microbiota, including opportunistic and pathogenic microorganisms. Regarding the safety of probiotic microorganisms, it is recommended that probiotic microorganisms must not harbour genetic resistance determinants, which encode resistance against clinically used antimicrobials. Thus, in a clinical setting the absence of transferable resistance genes is important information if a probiotic is intended for such use (Ammor et al 2007).
It might be argued that probiotic strains which are intrinsically resistant to drug(s) being administered might be of value to patients receiving antibiotic(s). Gould and Short (2008), examined the susceptibility pattern of organisms in two commercially available probiotic products. The authors found that the strains isolated from these products were susceptible *in vitro* to many of the antibiotics used to treat AAC and CDAD. They concluded that the bacteria contained in these products are unlikely to have an effect *in vivo*. To the best of our

knowledge, administration of resistant probiotics, either prophylactically or therapeutically, to AAD or CDAD-prone patients, has never been attempted

VIII. Benefit and Risk characterization

Clinical relevance / implications

VKM's previous assessments of probiotic supplementation, especially LGG, concerned the use of LGG in infant formula and food (www.vkm.no), and the major question was the possible long-term effects from factors that affect the establishment of intestinal microbiota in early infancy. Although several reports demonstrate possible beneficial health effects of probiotic supplementation, especially for the treatment of rotavirus-associated diarrhoea, the Scientific Committee consider that these positive effects do not outweigh the potential problems which could be associated with the artificially-introduced influence of probiotics on the development of the infants' internal ecosystem (www.vkm.no).

The present opinion is related to the general use of products supplemented with probiotic microorganisms for the seriously ill and hospitalized patients, and possible hazards connected with this practice.

In the following studies concerning probiotic supplementation in hospital patients suffering from acute pancreatitis, *C. difficile* infection and non alcoholic fatty liver disease (NAFLD) is presented. Furthermore, supplementation with probiotic bacteria in critically ill children, i.e. children in intensive care is discussed. Finally, the use of probiotics in patients with diarrhoea, *Helicobacter pylori* infection and inflammatory bowel disease is mentioned, as well as in patients with AIDS, urogenital infections, and small intestinal bacterial overgrowth.

Much of attention is focused upon a large study on probiotic administration to patients with acute pancreatitis (PROPATRIA). Acute pancreatitis is a life-threatening disease in which secondary infection is an important risk factor for death. The hypothesis was that probiotics could ameliorate the risk of infection. This study was very well-planned and conducted, and therefore the Scientific Steering Committee put special emphasis on the results when discussing the use of probiotics in seriously ill patients. Since only few probiotic strains have been subjected to exhaustive safety tests, the Scientific Steering Committee have no means of knowing which characteristics of concern in one probiotic strain may be present in another strain.

Probiotic strains used in some of the studies mentioned in this opinion are not yet on the Norwegian market. On the other hand, new products are constantly emerging, including products with probiotic strains novel to the Norwegian market, and in order not to limit the future usefulness of this report by restricting this risk assessment to strains presently marketed in Norway, they are included in the assessment.

Acute pancreatitis

Acute pancreatitis is a serious disease with high mortality, especially when the inflammation leads to necrosis of pancreatic and peripancreatic tissues. Provided that the necrosis remains sterile, multiple organ failure does not develop. However, should the necrosis become infected, multiple organ failure may develop, and surgical removal of necrotic tissue may become necessary. Systemic antibiotic prophylaxis has been used for some time as a measure to prevent secondary infections in acute pancreatitis, and the topic is still hotly discussed by clinicians. A recent meta-analysis concluded that although prophylactic treatment with

antibiotics is associated with a significant reduction in pancreatic or peripancreatic infection, non-pancreatic infection, and length of hospital stay, it does not prevent death nor the need for surgical intervention in acute necrotizing pancreatitis (Xu & Cai 2008). Routinely, antimicrobials are used mainly on demand for established infection, and there is a clear need for prophylactic strategies that reduce the high incidence of serious infectious complications in patients with acute pancreatitis.
Enteral nutrition is often used in critically ill patients because it is believed to reduce translocation and systemic spread of intestinal bacteria. Probiotics are sometimes added to the enteral feeding, with the aim of reducing overgrowth of other bacteria in the small-bowel, restoring gastrointestinal barrier function, and modulating the immune system (Bengmark 1998; Guarner & Malagelada 2003). A possibly possible enhancement of beneficial effect has been postulated if the enteral feeding contains both probiotics and prebiotics in combination (synbiotics). Probiotics appeared to reduce infectious complications in several clinical studies in patients undergoing elective abdominal operations (Rayes *et al.*, 2005; Rayes *et al.*, 2007) and in patients with acute pancreatitis (Olah *et al.*, 2002; Olah *et al.*, 2007).
In the 14 randomized clinical trials reviewed by (van Santvoort *et al.*, 2008), 9 studies showed a significant decrease of total infectious complications in the patients treated with probiotics, whereas 5 studies could not demonstrate such an effect. Bacterial infections were significantly decreased in the groups that were given synbiotics (probiotic bacteria + prebiotic carbohydrates). Although all these studies were small and individually inconclusive, the review paper concluded that the use of prebiotics might enhance the effect of probiotics and may even be a prerequisite for clinical efficacy of some probiotics strains.

To prove the concept of benefit of synbiotics in severe acute pancreatitis, a large, nationwide, multicentre, randomised, double-blind, placebo-controlled trial (the PRObiotics in PAncreatitis TRIAls (PROPATRIA)), was performed in the Netherlands.

The PROPATRIA-study (Besselink et al., 2008):
Methods: Patients with predicted severe acute pancreatitis were randomly assigned, within 72 h of onset of symptoms, to receive a multispecies probiotic preparation (n=153) or placebo (n=145), administered enterally (as an adjunct to enteral nutrition) twice daily for 28 days. The primary endpoint was infectious complications, i. e., infected pancreatic necrosis, bacteraemia, pneumonia, urosepsis, or infected ascites, during admission and at 90-day follow-up.
Findings: Infectious complications occurred in 46 (30%) patients in the probiotics group and in 41 (28%) of those in the placebo group (relative risk 1·06, 95% CI 0·75–1·51). However, twenty-four (16%) patients in the probiotics group died, compared with nine (6%) in the placebo group (relative risk 2·53, 95% CI 1·22–5·25). Nine patients in the probiotics group developed bowel ischaemia (eight with fatal outcome), compared with none in the placebo group (p=0·004).
Conclusions: In patients with predicted severe acute pancreatitis, probiotic prophylaxis with this combination of probiotic strains did not reduce the risk of infectious complications and was associated with an increased risk of mortality. Therefore probiotic prophylaxis should not be administered to this category of patients.

Several comments on the study have been published. (Sand & Nordback 2008) and (Soeters 2008) emphasise that several patients in PROPATRIA had indications of organ failure and probably therefore severe splanchnic hypoperfusion. The great quantity of bacteria administered may have aggravated mucosal inflammation, already present due to the pancreatitis, and increased the demand for substrate and oxygen at a site where the supply is

already marginal. Hence, intestinal perforation (necrosis) and inflammation occurred close to the site where nutrition and prebiotics were delivered to the duodenum. However, the bacteria responsible for the infectious complications were ‘‘normal’’ non-probiotic bacteria present in the gut.

Soeters (Soeters 2008) also stresses the fact that a major part of the excess mortality in the probiotics group occurred within 14 days and that organ failure in the patients developing bowel necrosis occurred, with one exception, after 1 or 2 days, as if there was an instantaneous effect of the regimen. Both the probiotic and the placebo groups received prebiotics. The role of prebiotics is uncertain, but apparently, prebiotics alone did no harm, as bowel necrosis was not diagnosed and mortality was low in the placebo group. It was the combination of pro- and prebiotics that yielded the deleterious results and it is unclear what would have happened if probiotics had been given alone.

Case reports of acute intestinal necrosis have been previously described in the presence of patent vasculature to the gastrointestinal tract and complications have been related to bacterial overgrowth, achlorhydria, malnutrition, old age, alcoholism, critical illness, and several other debilitating conditions. Intestinal necrosis at the site of infusion from a jejunal feeding tube, as was seen in PROPATRIA, has also been described previously. Enteral nutrition containing probiotics that has bypassed normal digestion in the oral cavity, stomach and duodenum is possibly particularly damaging to the intestine.
The comments seem to agree that similar complications most probably occurred in patients that are critically ill due to causes other than acute pancreatitis. Administration of probiotics through jejunal feeding may have an additional deleterious effect. Thus it is the opinion of the Norwegian Scientific Committee that probiotics should not be supplied by jejunal feeding tube to critically ill patients.

***Antibiotic-associated diarrhoea (AAD), including Clostridium difficile* infection (CDAD)**
Over the years, nearly all probiotics have been clinically tested for prevention and treatment of AAD and acute and recurrent *C. difficile* diarrhoea.

a. Prevention
So far, however, there are few, if any, indications that probiotics can prevent AAD and CDAD (Surawicz 2008; Pillai & Nelson 2008).

b. Treatment
There have been many publications stating that some probiotics (especially *L. rhamnosus* GG and *S. boulardii*) may have a therapeutic effect, but several studies have given negative results. It should be underlined that “various probiotics have variable efficacy” (Surawicz 2008) and that “they should be used with caution in patients who have compromise of either the immune system or the integrity of the intestinal mucosa, and in the presence of a central venous catheter” (Doron *et al.,* 2008). Further; “given the potential for complications in debilitated or immunosppressed patients, the risks may outweigh benefits……” (Segarra-Newnham 2007). In all recent reviews, statements similar to the following can be found: “More studies are needed to define further their efficacies, roles and indications (Surawicz 2008; Doron *et al.,* 2008).
In conclusion, although some studies indicate a prophylactic effect of probiotic supplementation on AAD and CDAD, there is a general agreement that probiotics are contraindicated in critically ill patients. It is the opinion of the Scientific Steering Committee that as for therapeutic effects, given the potential for complications in debilitated or immunosuppressed patients, the potential risks considerably outweigh the benefits.

Non-alcoholic fatty liver disease (NAFLD)
Uncontrolled studies indicate that probiotics are well tolerated, can improve liver function, and may reduce the marker for lipid peroxidation. However, the lack of controlled studies makes it impossible to reach a conclusion regarding the effect of probiotics on NAFLD and non-alcoholic steatohepatitis (NASH) (Lirussi *et al.*, 2007).

Diarrhoea, unrelated to antibiotic treatment
Probiotic bacteria have been widely used in cases of diarrhoea, in both children and adults, with somewhat conflicting results, but overall there are no documented adverse effects. Some authors report shortening of hospitalization in those given probiotics and a favourable influence on the course of the illness (Kaila *et al.*, 1992; Isolauri *et al.*, 1995; Katz 2006; Wenus *et al.*, 2008).
Diarrhoea is frequent in the critically ill, especially in cases with sepsis and hypoalbuminaemia, and during treatment with enteral nutrition. The standard treatment consists of liberal rehydration, replacement of electrolyte loss, use of anti-diarrhoeal remedies, and continuation with enteral nutrition. The benefit of enteral supplementation with soluble fibre, probiotics, or prebiotics is not clear (Wiesen *et al.*, 2006).

Paediatric patients
The two previous reports on probiotics (LGG) (www.vkm.no) primarily addressed their use in healthy infants and small children. In the current opinion, the Scientific Committee consider hospitalized children. Children are generally not hospitalized nowadays unless they are seriously ill. Two important reports from paediatric units concern children at risk: preterm neonates and paediatric patients in intensive care. (Deshpande *et al.*, 2007) conclude in a review that probiotics may reduce the risk of necrotizing enterocolitis (NEC) in preterm infants. However, the need for short- and long-term safety assessment in large trials is imperative. Many questions as to dose, duration of supplementation and type of probiotic agents are still unanswered. The conclusion from the other study comprising children in intensive care (Honeycutt *et al.*, 2007) was: "The results of this preliminary investigation were unexpected but important in view of the increased use of probiotic preparations in medically fragile pediatric patients". In this randomized, placebo-controlled trial, *L. rhamnosus* strain GG was not shown to be effective in reducing the incidence of nosocomial infections. Disturbingly, a statistically non-significant trend towards an increase in infection was seen (four vs. 11). Further studies with a larger patient population are needed to establish both safety and efficacy of probiotic in paediatric critical care.
All the studies on probiotic supplementation aimed at prevention or treatment of atopic dermatitis in children deal with infants and small children who are healthy apart from their allergic disposition. Thus, these studies are not pertinent in assessing the effect on critically ill patients. Moreover, even the possibility of preventing atopic dermatitis or other allergic conditions would not justify the use of such preventive measures if there was the slightest possibility of them exerting a harmful effect on critically ill children.

Inflammatory bowel disease (IBD)
It is commonly accepted that the intestinal microbiota play an important role in the pathogenesis of inflammatory bowel disease (IBD). Studies suggest that the composition of the flora is altered, and there are elevated levels of some 'pathogenic' bacteria, and reduced levels of *Bifidobacterium* and *Lactobacillus*. Additionally, high concentrations of bacteria are found in contact with the mucosal membrane (increased amounts of adherent bacteria) (Rolfe *et al.*, 2006). No unequivocal effects on the illness have been demonstrated in the many

attempts to alter this biotic imbalance by use of antibiotic and probiotic treatments (Ewaschuk *et al.,* 2006; Seksik *et al.,* 2006; Subramanian *et al.,* 2006; Jones & Foxx-Orenstein 2007). A review of three studies examining the possible effect of probiotics on the general postoperative outcome in patients with Crohn's disease, concludes that "… probiotics have no proven role in postoperative prophylaxis" (Froehlich *et al.,* 2007). One of these studies observed that after administration of *L. johnsonii* as probiotic for 12 weeks, the percentage of endoscopic severe recurrence was 19% in the treatment group compared with 9% in the placebo group, which is a near significant side effect (Van Gossum *et al.,* 2007).

Nonpathogenic *Escherichia coli* strain Nissle 1917 has been used in several European countries as a probiotic drug for the treatment of IBD. In ulcerative colitis its prophylactic efficacy appears comparable to that of mesalazine. The precise mechanism of action remains unclear (Kruis *et al.,* 2004).

***H. pylori* infection**

Although *H. pylori* is not eradicated by probiotic treatment, the amount of bacteria may be reduced, and, in combination with antibiotics, may increase eradication rate and reduce the side-effects of treatment (Gotteland *et al.,* 2006). Probiotics have also been used as a supplement to ordinary triple-treatment for *H. pylori*-eradication, but without any convincing effect (Park *et al.,* 2007).

AIDS and Hodgkin's disease

A report on the isolation of *L. acidophilus* from the bacteraemia in a patient suffering from AIDS and Hodgkin's disease, who had been taking a probiotic product, concluded that care should be taken with administering probiotics to patients with 'significant medical problems', including oncology patients (Ledoux *et al.,* 2006). However, their conclusions are speculative since the isolated strain was not matched by molecular methods with the strain used in the product, and could have been part of the patient's own flora.

Urogenital infections

Some recent reviews (Barrons & Tassone 2008); (Falagas *et al.,* 2007; Betsi *et al.,* 2008) of the use of probiotics for various urogenital infections have pointed out lack of efficacy as the major result, especially for infections caused by *Candida*, whereas bacterial vaginitis seems to be more likely to respond to probiotic administration. No negative reactions were mentioned and there seems to have been no focus on this aspect in such patients.

Small Intestinal Bacterial Overgrowth

Experimental animal studies indicate that probiotics can improve the mucosal barrier, have antibacterial properties, and have immunomodulatory and anti-inflammatory effects, all of which can be positive against bacterial overgrowth in the small intestine and against small intestinal failure. However, positive effects in patients with these conditions have not been definitively demonstrated (Quigley & Quera 2006).

IX- Data gaps

The following data gaps listed below have been identified:

- Effect on intestinal cells (enterocytes)
- The role of probiotic microoranisms in plaque formation and chronic lesions (rheumatoid arthritis)
- The role of probiotics in platelet aggrevation

- Information on whether, and to what extent, probiotic strains contain enzymes capable of splitting sulphate conjugates
- Information regarding degradation of mucin

X- Answers to the questions

1) What benefits can be derived from the use of probiotics, or products containing probiotics, by different groups of hospital patients? For example:

- children with serious or chronic illnesses,
- pregnant women (e.g. those with hyperemesis, with enteral nutrition being delivered directly to the small intestine),
- patients with chronic illnesses, particularly those with intestinal diseases,
- the seriously ill (e.g. bone marrow transplant patients),
- immunocompromised patients,
- recently operated patients.

- There is some evidence of a beneficial effect of probiotic bacteria on diarrhoea in hospitalized children with infectious diarrhoea, especially virus-associated diarrhoea. Furthermore, a favourable effect on NEC (necrotizing enterocolitis) in preterm babies is reported in some studies, but not in all.
- The literature on pregnant women with hyperemesis supplemented with probiotics is scarce and thus no firm conclusion can be drawn concerning this patient group.
- There is no scientific evidence showing benefit from probiotic supplementation in critically ill or chronically ill patients with gastrointestinal disease.
- There is no evidence of beneficial effect on critically ill patients such as bone marrow and other transplant patients.
- Newly operated patients are in a critical situation and should probably, in this context, be treated similarly to those with critical illness. No reports strongly support the use of probiotics in this category of patients.

2) Are there any contraindications for the use of probiotics, or products containing probiotics, for different groups of hospital patients? For example:

- children with serious or chronic illnesses
- pregnant women (e.g. those with hyperemesis, with enteral nutrition being delivered directly to the small intestine),
- patients with chronic illnesses, particularly those with intestinal diseases,
- the seriously ill (e.g. bone marrow transplant patients),
- immunocompromised patients,
- recently operated patients.

- There are reports on increased infections in critically ill hospitalized children when given probiotics. As the positive effects of probiotics in hospitalized children are dubious, and as some adverse effects have been reported, the administration of probiotics to this vulnerable group of children is unadvisable. Whilst many unanswered questions still remain concerning dose, type of strain, length of supplementation, etc. caution should be employed in treating this very vulnerable group of children.
- There is no literature concerning administration of probiotics to hyperemesis patients. However, the PROPATRIA study indicates that enteral nutrition combined with probiotics delivered directly into the duodenum could be dangerous. Thus the Scientific Steering Committee also considers this treatment potentially dangerous in this critically ill group of patients.

- There are strong contraindications for the use of probiotics in hospital patients receiving enteral nutrition directly into duodenum through a duodenal tube.
- Probiotics should not be given to critically ill patients receiving parenteral nutrition.
  - Recently operated patients given parenteral nutrition are in a critical situation (as long as their intestines are unable to handle enteral nutrients). They should therefore probably not have probiotics administered.

3) Is there any risk that the use of probiotics can result in an increased development in antimicrobial resistance? For example, can the use of probiotics be a reason for, or result in, an increase in the number of nosocomial infections?

- There are an increasing number of reports concerning acquired resistance genes in probiotic and potentially probiotic microorganisms.
  There are similarities in these gene determinants in bacteria of human origin and probiotic microorganisms, which may suggest the spread of resistance genes between commensal microorganisms in the complex ecosystem.

- Intake of probiotic microorganisms that bear mobile antimicrobial resistance genes may increase the risk of the transfer of such genes to the resident microbiota and thereby increase the problem of treating nosocomial infections.

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