INNER HEALTH

# High strength probitics for targeted support during antibiotic treatment

Antibiotics disrupt a balanced microbiome by altering the quantity and diversity of commensal species of native bacteria present in the gut (1). This document will examine the role antibiotic use plays in causing perturbations to gut health and the role specific probiotic strains can play in reducing antibiotic resistance and in restoring health to the gut.

This document will investigate & explain:

1. **Antibiotic prescribing practices**
   - Benefits of medically prescribed antibiotics
   - Antibiotic use in Australia & New Zealand
   - Antibiotic prescribing and the rise of antibiotic resistance
2. **What is antibiotic resistance?**
   - Role of antibiotic prescribing practices
   - How antibiotic resistance develops
   - Antibiotic resistance mechanisms
3. **Antibiotics & the human gut microbiome**
   - Understanding the human microbiome
   - How antibiotics disrupt microbiome balance
4. **Antibiotic alterations to healthy gut bacteria**
   - Consequences of antibiotic treatment
   - Acute and chronic antibiotic use
   - The effect of antibiotic course dose & duration on antibiotic resistance

## Clinical Features

- Taken alongside antibiotics, clinically indicated probiotic strains work to restore gut health and reduce antibiotic resistance.
- LGG® increases common native commensal bacteria and suppresses antibiotic resistant bacteria.
- SB reduces the incidence of antibiotic associated diarrhoea in at risk people.

## Therapeutic Activity

**Lactobacillus rhamnosus LGG®**

LGG® has been shown in research to restore commensal flora and reduce antibiotic resistant bacteria spread (1,31,32).

**Saccharomyces cerevisiae (boulardii) SB**

SB reduces the incidence of antibiotic associated diarrhoea in at risk people (27).

## Dosing & Indications

**Lactobacillus rhamnosus LGG®**
Restore and protect native commensal species of beneficial bacteria. Reduce antibiotic resistance.
**Adults:** 20 Billion CFU daily

**Saccharomyces cerevisiae (boulardii) SB**
Reduce pathogenic organism overgrowth.
**Adults:** 15 Billion CFU daily (750mg)

## 1. Antibiotic prescribing practices

### Benefits of medically prescribed antibiotics

Antibiotics contribute positively to a global reduction in morbidity and mortality as they are the first line therapy to treat bacterial infections that could otherwise occasion death. Dispensed for the treatment of bacterial infections during acute infective episodes, or prophylactically for surgery patients and the immunocompromised, the medicinal viability of antibiotic drugs is paramount for the survival of millions of people worldwide every year.

### Antibiotic use in Australia

Australia has one of the highest rates of antibiotic use among countries with comparable health systems (2).

Over 30 million antibiotic prescriptions are filled in Australia each year, with 50% of antibiotic users being dispensed a repeat prescription within10 days (2,3). The high frequency of antibiotic use has led to many of the bacteria that cause infections to become increasingly resistant to existing antibiotics (4).

### Antibiotic prescribing & the rise of antibiotic resistance

Medically prescribed antibiotic treatments such as penicillins, sulfa drugs, macrolides, aminoglycosides, quinolones, cephalosporins and carbapenems; are vital for the management and prevention of life-threatening infections (2). Unfortunately, a growing list of infections are becoming harder to treat as antibiotics become less effective due to the growing risk of antibiotic resistance (3). These infections include pneumonia, tuberculosis, septicaemia, gonorrhoea and some foodborne diseases. With the rapid rise of antibiotic resistant organisms the burden of disease risk to the global population increases exponentially.

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## 2. What is antibiotic resistance?

**Role of antibiotic prescribing practices**

Antibiotics are medicines used specifically in the prevention and treatment of bacterial infections. When an antibiotic is used to treat a bacterial infection, typically most of the bacteria are killed. Antibiotic resistance occurs when bacteria change in response to the use of these medicines. When a bacterium cannot be killed by an antibiotic, it is known to become antibiotic resistant. Bacteria, not humans or animals, become or antibiotic resistant (5).

Antibiotic resistance is a kind of Antimicrobial Resistance (AMR). AMR happens when microorganisms (including bacteria, fungi, viruses and parasites) change when exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics) (6). While being a natural consequence of the use of these medicines over time, rates of AMR are increasing due to additional factors such as excessive usage and prescription of some medications, the inappropriate use of some medications, and the presence of substandard pharmaceuticals in the market. Among one of the top three threats to global health as outlined by the World Health Organisation, antibiotic resistance casts a shadow over the place antibiotics hold as lifesaving medicines in the fight against bacterial pathogens (6).

**How antibiotic resistance develops**

When a bacterium has an advantage that assists in their survival in the presence of antibiotics, it lives to pass on its advantages to subsequent generations, as a result creating antibiotic resistant bacteria (7).

There are two main types of antibiotic resistance – intrinsic resistance and acquired resistance.

1. **Intrinsic resistance** occurs when bacteria survive antibiotic treatment due to an inbuilt resistance, e.g. penicillin works by killing the cell walls of bacteria, but some bacteria do not have cell walls, meaning they cannot be destroyed by the drug (7).
2. **Acquired resistance** occurs when a bacterium develops resistance through the survival of a gene trait through selective pressure, or through the transfer of genes from bacteria that are already resistant. Selective pressure can occur as a result of frequent antibiotic use over long periods of time putting pressure on pathogenic bacteria, causing resistances to spread. Gene transfer occurs as a consequence of the bacterial lifecycle, and in the case of the transferal of resistant genes, leads to the passive acceptance of this trait by otherwise non-affected bacterium (7).

**Antibiotic resistance mechanisms**

Mechanisms of drug resistance fall into four broad categories, including (8):

1. Drug inactivation/alteration
2. Modification of drug binding sites/targets
3. Changes in cell permeability resulting in reduce intracellular drug accumulation
4. Biofilm formation

**1. Drug inactivation/alteration**

Many bacteria produce enzymes that irreversibly modify and inactivate the antibiotics, such as beta-lactamases, aminoglycoside modifying enzymes or chloramphenicol acetyltransferases e.g. beta-lactamases hydrolyze the beta-lactam ring present in all beta-lactams, meaning all penicillins, cephalosporins, monobactams and carbapenems can be affected by this process (8).

**2. Modifications of drug binding sites**

Some resistant bacteria avoid recognition by antimicrobial agents by modifying their target sites e.g. the mutation of gene encoding for specific penicillin-binding proteins (enzymes typically anchored on the cytomplasmic membrane of the bacterial cell wall that function in assembly and control of the latter stages of the cell wall building) having a low affinity for beta-lactam antibiotics, thus enabling the survival of *S.aureus* in an otherwise hostile environment (8).

3. **Reduced intracellular drug accumulation**

   The balance of antibiotic uptake and elimination determines the susceptibility of bacteria to a particular drug. Thus, reducing the amount of antibiotic able to pass through the bacterial cell membrane is one strategy used by bacteria to develop antibiotic resistance. Mechanisms by which bacteria achieve this include the occurrence of diminished protein channels on the bacterial outer membrane to decrease drug entry and/or the presence of efflux pumps to decrease the amount of drug accumulated within the cells (8).

4. **Biofilm formation**

   Under the conditions created via biofilm production, it is difficult to eliminate bacteria using conventional antibiotics as the matrix of the biofilm provides a mechanical and biochemical shield that provides the condition necessary to attenuate the activity of the drug (8).

## 3. Antibiotics & the human gut microbiome

### Understanding human gut microbiome

The human microbiome consists tens of trillions of symbiotic microbial cells, comprising of around 1000 species of bacteria. Composed of a diverse population of commensal bacterial species made up of both beneficial and pathogenic strains, the relative abundance of beneficial species provides a homeostatic balance to the microbiome with the aim of providing resistance against the colonization of disease-causing pathogenic species (9).

The dominant bacterial phyla in the adult human gut are Firmicutes, Bacteroidetes and Proteobacteria (10). Other phyla make up a smaller percentage and these include Actinobacteria, Fusobacteria, and Verrucomicrobia (11). Practically all surfaces of the human body exposed to the environment are normally inhabited by microorganisms. The intestine constitutes an especially rich and diverse microbial habitat. Approximately 800 to 1000 different bacterial species and more than 7000 different strains inhabit the gastrointestinal tract (4). The significance of a healthy intestinal microbiota cannot be underestimated, as it performs a number of key functions that are essential to the wellbeing of the host. These functions include the production of short-chain fatty acids (SCFAs) such as butyrate, immune system responsiveness, nutrient and drug processing, and a homeostatic influence on glucose and lipid metabolism (12)

Several antibiotics are active specifically against anaerobic bacteria that dominate in the human intestinal microbiota (Table 1). Broad spectrum antibiotics carry higher risks of side effects than narrow spectrum (13,14). Four of the five most commonly used antibiotics in Australia are broad spectrum, namely amoxicillin-clavulanate (Co-amoxiclav), cefazolin (Cephalosporin), amoxicillin and doxycycline (15).

According to the literature, one side effect of an antibiotic treatment course is increased susceptibility to a range of bacterial infections (2). The use of multiple or long courses of antibiotics, can cause disruption of microbiome homeostasis leading to an overgrowth of pathogenic microorganisms - making those individuals exposed to these therapeutic interventions susceptible to symptoms of gut and microbiome dysfunction (8).

### How antibiotics disrupt microbiome balance

Treatment with antibiotics is considered one of the most extreme perturbations to the human microbiome (16). Antibiotics disrupt a balanced microbiome by altering the quantity and diversity of bacteria species present in the gut (2). Persistent negative effects associated with a single course of antibiotics have been demonstrated at least four years after exposure to antibiotics. (2,17)

Antibiotic resistant bacteria spread through the microbiome when microorganism diversity is reduced through antibiotic use. Even standard courses of antibiotics dramatically reduce the microbiomes diversity and can cause transitions to dysbiotic states that can remain permanent (16). When microbiome diversity is reduced, antibiotic resistant species transfer antibiotic resistant genes to other native species, therefore promoting the continued spread of antibiotic resistant genes throughout the normal microbiome (8).

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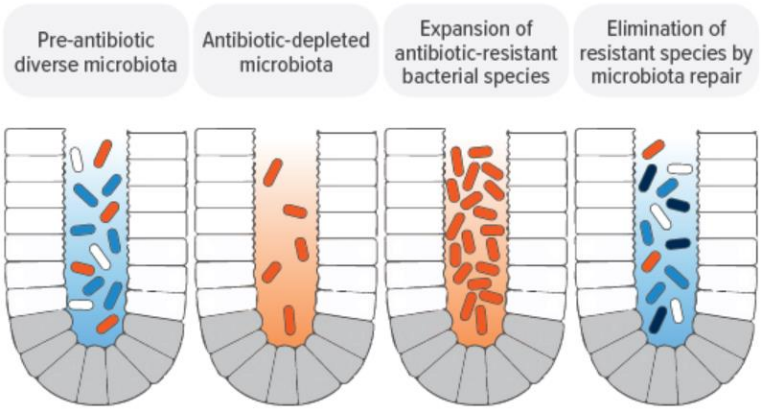


Figure 1: Antibiotic treatment eliminates many commensal bacteria species from the gut lumen and reduces antimicrobial defences (18)

## 4. Antibiotic alterations to healthy gut bacteria

**Consequences of Antibiotic Treatment**

Alexander Fleming's discovery of the potency of Penicillium notatum against Staphylococcus bacteria in 1928 instigated a dramatic and powerful shift in the medical world (19). The lives of millions have been saved due to the discovery of penicillin, and the subsequent development of other antibiotic medications.

**Acute & chronic antibiotic use**

Antibiotic use can result in both acute and chronic alterations to the quantity and diversity of the normal intestinal microbiota, as they not only affect the target pathogen, but also the commensal bacteria of the human host. Persistent negative effects associated with a single course of antibiotics have been demonstrated at least four years after exposure to antibiotics (4,17). An imbalance in the commensal gut microbiota due to antibiotic administration can result in intestinal problems, such as antibiotic-associated diarrhoea (AAD), taste disturbances, abdominal pain, as well as overgrowth of opportunistic, pathogenic bacteria and fungi (20,11).

### Key Insights

**Top conditions for antibiotic prescribing in Australia** (3):

- *Upper respiratory tract infections*
- *Bronchitis*
- *Urinary tract infections*
- *Sinusitis*
- *Otitis media*
- *Tonsillitis*
- *Pneumonia*

Table 1: Effect of specific antibiotics on gut microbiota.

| Factor | Effects |
|---|---|
| Fluroquinolones & $\beta$-lactams | Decreases microbial diversity, reshapes the microbiota in favour of resistant bacteria strains in the long term. |
| Clindamycin | Reduces resistance to colonization by pathogens, increases risk of *C.diff* colitis, gastritis, bloating, diarrhoea and intestinal pain. |
| Moxifloxacin, cefazolin, ampicillin/sulbactam, amoxicillin, penicillin. clindamycin | Qualitative and quantitative changes in microbiota, increased risk of opportunistic infection by Escherichia spp. & Klebsiella spp. |
| Antibiotic treatment | Deactivates mucins, immune defence modifications caused by alterations in intestinal commensals. Promotion of viral, allergic and opportunistic infections (including *Salmonella typhimurium, C.diff* and *E. coli*). |

Adapted from Dudek-Wincher, Junka & Bartoszewicz, 2018 (21)

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# High strength probitics for targeted support during antibiotic treatment

**The effect of antibiotic course dose & duration on antibiotic resistance**

More is not always better when it comes to antibiotics (6), as new research suggests that short courses are usually equally as effective as longer courses for most common uncomplicated infections treated in the community setting (7).

Antibiotic use can result in both acute and chronic alterations to the quantity and diversity of normal intestinal microbiota, as well as mucous barrier destabilisation, with persistent effects being demonstrated for extended periods following antibiotic exposure (17).

Modern approaches to antibiotic resistance now suggest prolonged exposure to antibiotics provides selective pressure to drive antimicrobial resistance; meaning in part that longer course are more likely to result in the emergence of resistant bacteria than short courses (21).

With over one in five antibiotic users being dispensed a repeat prescription (22), it is also important to note that the frequency of courses is also likely to contribute the highest degree of resistances forming than from any other cause (6). Disturbingly, Australian research also suggests that only 24% of people prescribed an antibacterial have an indication recorded for their prescription, and of these people, 60% were prescribed antibiotics for colds and other infections where antibiotics are not generally recommended (22).

## Key Insights

**How antibiotic use drives opportunistic pathogens**

Opportunistic infections are caused by bacterial species that are mostly small population commensal species, but in the right conditions can also identify as opportunistic pathogens.

For example *Streptococcus pneumonia*, a bacteria carried mainly by children can in the wrong circumstance cause acute otitis media, meningitis, bacteraemia and pneumonia in the same population (7).

## Clinical Features

**Restoring & protecting beneficial native commensals**

Ongoing studies are identifying heathy commensal bacterial species are the key to a healthy microbiome (23). As a result, restoring native beneficial gut flora is now understood to be vital to the reestablishment of microbiome homeostasis following antibiotic use.

LGG® has been shown at a dose of 20 Billion CFU to support digestive function via the modulation of key commensal gene expression, to directly increase many of the most common commensal bacterial genus found in the human gut including *Roseburia, Prevotella, Eubacterium, Coprococcus Ruminococcus and Blautia* genera (24,25). The mechanisms for this manipulation include the improvement of motility to allow GI mucosal penetration, and an increase in butyrate production by the bacteria, leading to an increase in fuel availability for beneficial commensal bacteria (26). Re-establishing microbiome-mediated colonization resistance after antibiotic treatment could markedly reduce infections, particularly those caused by antibiotic resistant bacteria (23).

**Inhibiting pathogenic organism overgrowth**

Pathogenic organism overgrowth is a common complication of antibiotic use (27).

LGG® has been shown in hospital run clinical trials to reduce the development of Vancomycin-resistant enterococci (VRE) in children (23) and adults (24). LGG® may reduce VRE, and the development of other pathogens such as *Clostridium difficile*, by competitively targeting colonisation sites, competing with VRE for fuel use, and through their direct antimicrobial and pH modification activities (24). One randomised clinical trial found that LGG® temporarily eliminated vancomycin resistant enterococci (VRE) colonisation and has the potential to eradicate VRE in carriers, as well as increase the pool of desirable bacteria in the gastrointestinal tract. Twenty-seven VRE positive subjects were randomly assigned to either a treatment group (receiving 100g daily of yoghurt containing LGG® for four weeks) or a control group (receiving standard pasteurised yoghurt). Faecal samples were obtained three times at weekly intervals. Treated patients were tested for VRE again at eight weeks. Patients in the control group who had failed to clear VRE after four weeks were then given yoghurt containing LGG® for 4

weeks, as an open continuation to the trial (24). Of the 27 patients enrolled, 23 completed the study. All 11 patients in the treatment group who completed the study cleared VRE. Twelve control subjects completed the study with only one clearing VRE and 11 remained VRE-positive. Eight of these 11 patients were subsequently crossed-over to receive LGG® yoghurt, with all clearing the remaining VRE within four weeks (24).

A Cochrane Review of 23 randomised, controlled trials which included 4,213 subjects concluded there is favourable evidence showing that the administration of LGG® is a safe and effective intervention for preventing CDI associated diarrhoea during antibiotic use (28).

*Saccharomyces boulardii* (SB) has been shown in meta-analysis and systematic reviews to inhibit pathogenic organism overgrowth. The effects of SB have been shown to be dose dependent, with larger studies (29) (n>1000) detailing a dose of 15 billion CFU (750mg) SB microorganisms per day to be more effective than smaller doses of 5-10 billion CFU (250mg-500mg) per day (27,29).

## Patient Warning Statements

**LIFESTAGE & CONDITION**

- **Pregnancy:** appropriate for use (30).
- **Breastfeeding:** appropriate or use (30).

**CAUTIONS & CONTRAINDICATIONS**

- **Severely ill and**/or **immunocompromised patients**: *Lactobacillus* bacteraemia and sepsis have been reported in severely ill and/or immunocompromised patients consuming probiotic such as *Lactobacillus*, though this is a very rare finding (30).
- **Short bowel syndrome**: Patients with short bowel syndrome might be predisposed to pathogenic infection from lactobacillus. This might be due to impaired gut integrity in patients with short bowel syndrome. Use only under medical supervision in patients with this condition (30).

**DRUG/HERB/NUTRIENT INTERACTIONS**

- **Antibiotics**: separate antibiotic medications from probiotics by two hours.
- **Immunosuppressant medications**: Theoretically, *Lactobacillus* could cause infection in patients taking medications that suppress the immune system. These include cyclosporine, tacrolimus, azathioprine, and cancer chemotherapeutic agents like cyclophosphamide and cisplatin. Use only under medical supervision in these patients (30).

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