# **Recent Studies on Gut Microbiome and Antimicrobial Resistance**

# **STUDIES**

## 1. Antibiotic Resistance In Lactic Acid Bacteria

Bacterial resistance to antibiotics is an emerging public concern that may compromise the efficacy of agents used for the treatment of infectious diseases.

This review article presents an overview of the LAB antibiotic resistance and some methods which determine the characteristic, as per the FAO/OMS guideline for testing food-related bacteria and probiotics for resistance patterns.

Source: De Yi Tong, Department Of Veterinary And Agricultural Sciences, University Of Melbourne, Australia. Antibiotic Resistance In Lactic Acid Bacteria. J Prob Health. 9:234 (2021). DOI: 10.35248/2329-8901.21.9.234

# 2. Antimicrobial Activity Of Bacillus Subtilis KATMIRA1933 And Bacillus Amyloliquefaciens B-1895 Against Staphylococcus Aureus Biofilms Isolated From Wound Infection

In this study, four clinical isolates of staphylococci species; two isolates of methicillin-resistant Staphylococcus aureus (MRSA) and two methicillinsensitive Staphylococcus aureus (MSSA) isolates were studied.

Researchers have found that the isolated staphylococci were highly resistant to the following antibiotics, amoxicillin, penicillin G, cefotaxime, and methicillin. Combinations of cefotaxime with the cell-free supernatants (CFS) of Bacillus subtilis KATMIRA1933 and Bacillus amyloliquefaciens B-1895, each one separately showed complementary activity against the tested staphylococci. The co-aggregation capability of the tested bacilli as beneficial bacteria against isolated staphylococci was also evaluated. The data showed a strong co-aggregation with scores (+ 3, + 4) which were reported between the bacilli strains and the isolated staphylococci. Furthermore, the CFS of bacilli strains showed an inhibitory effect against biofilm-associated MRSA and MSSA. These findings confirmed the ability of beneficial bacteria to compete with the pathogens at the site of colonization or for the source of nutrients and, eventually, lead to inhibition of the pathogens' capability of causing a wound infection. Such beneficial bacteria could play important role in future pharmaceutical and industrial applications.

Source: Ammar Algburi, Department Of Biotechnology, College Of Science And Department Of Scholarship And Cultural Relations, Presidency Of Diyala University, Baqubah, Iraq. Antimicrobial Activity Of Bacillus Subtilis KATMIRA1933 And Bacillus Amyloliquefaciens B-1895 Against Staphylococcus Aureus Biofilms Isolated From Wound Infection. Probiotics & Antimicro. Prot. 13, 125–134 (2021). <u>https://doi.org/10.1007/s12602-020-09673-4</u>

## 3. In Vitro Assessment Of Antimicrobial Efficacy Of The D-Tagatose And Lactobacilli-Based Synbiotic Preparations Against The Pathogenic Escherichia Coli And Salmonella Typhimurium

The study aimed to investigate the utilisation of *prebiotic D-tagatose* by *probiotic lactobacilli (L. rhamnosus GG, L. casei, L. acidophilus and L. fermentum)* and *enteric pathogens (E. coli and S. typhimurium)* to determine synbiotic potential of D-tagatose and lactobacilli combination. The antimicrobial efficacy of the synbiotic preparations (D-tagatose with lactobacillus) was assessed against selected pathogens in co-culture assays.

Scientists found that D-tagatose supported growth of selected lactobacilli, especially the L. rhamnosus GG and L. casei, but not the enteric pathogens. The tested synbiotic preparations completely inhibited growth of both the pathogens, even in the presence of D-glucose in co-cultures. The well-diffusion assay demonstrated the presence of antimicrobial activity as recorded by drop of culture pH. The study substantiated that D-tagatose could be an effective prebiotic component for formulation of potential synbiotic combinations with L. rhamnosus GG or L. casei that can be used as an alternative to antibiotics against enteric pathogens.

Source: Ashis Kumar Samanta, ICAR-National Institute Of Animal Nutrition And Physiology, Adugodi, Hosur Road, Bengaluru, India. Synbiotic Preparations Against The Pathogenic Escherichia Coli And Salmonella Typhimurium. International Journal Of Food Science & Technology, Volume56, Issue5, Special Issue: Microbiota, Probiotics And Prebiotics, May (2021), Pages 2156-2165. <u>https://Doi.Org/10.1111/ljfs.14909</u>

# 4. Genotyping Of Multi Drug Resistant Bacteroides Fragilis Group Of Clinical Isolates From Mangalore, South India

Bacteroides fragilis group, the most encountered anaerobic bacterium is emerging with resistance to antibiotics. This study explores the antibiogram and occurrence of resistance genes in isolates of B fragilis group from clinical samples.

Study result shows that ceftriaxone, cefoxitin, clindamycin and imipenem were the most resistant antimicrobials in E test method. *Metronidazole* has shown resistance in 7 strains in vitro while resistance nim genes were detected in 12 strains from 62 randomly selected isolates. Further, other resistance genes (cfiA, ermF and cepA) were expressed at 58%, 62.9% and 48.3% respectively, among these strains.

Source: Beena Antony, Department Of Microbiology, Father Muller Medical College, Kankanady, Mangalore, Karnataka, 575002, India. Genotyping Of Multi Drug Resistant Bacteroides Fragilis Group Of Clinical Isolates From Mangalore, South India. Indian Journal of Medical Microbiology, Volume 39, Issue 1, January (2021), Pages 19-23. https://doi.org/10.1016/j.ijmmb.2020.10.013

#### 5. Investigating Multi-Drug Resistant Acinetobacter Baumannii Isolates At A Tertiary Hospital In Pretoria, South Africa

In this study scientists have investigated the genetic determinants of *multi-drug resistant A. baumannii (MDRAB*) at a teaching hospital in Pretoria, South Africa.

Researchers found that seventy (70) out of 100 isolates which were collected, confirmed multi-drug resistant and were **blaOXA51** positive. Phenotypically, the isolates were resistant to almost all tested antibiotics. One isolate showed intermediate susceptibility to **tigecycline** while all were susceptible to **colistin**. **Oxacillinase gene blaOXA-23** was the most detected at 99% and only 1% was positive for **blaOXA-40**. For **Metallo betalactamases (MBL)**, **blaVIMwas** the most frequently detected at 86% and **blaSIM-1** at 3% was the least detected. Fifty-six isolates had the required gene combination for an active efflux pump. Further, the most prevalent was clone A at 69% of the isolates. **Colistin** and **tigecycline** were the most effective against investigated isolates.

Source: Noel-David Nogbou, Department Of Microbiological Pathology, Sefako Makgatho Health Sciences University, Pretoria, South Africa. Investigating Multi-Drug Resistant Acinetobacter Baumannii Isolates At A Tertiary Hospital In Pretoria, South Africa. Indian Journal of Medical Microbiology, Volume 39, Issue 2, April (2021), Pages 218-223. https://doi.org/10.1016/j.ijmmb.2021.03.005

# 6. Dynamics Of The Fecal Microbiome And Antimicrobial Resistome In Commercial Piglets During The Weaning Period

The aim of this study was to characterize the alteration of the fecal microbiome and antimicrobial resistance (AMR) determinants in 24 piglets at day 3 pre-weaning (D. – 3), weaning day (D.0), days 3 (D.3) and 8 post-weaning (D.8), using whole-genome shotgun sequencing.

Researchers have observed distinct clusters of microbiomes and AMR determinants at D.8 when **Prevotella (20.9%)** was the major genus, whereas at D. – 3–D.3, **Alistipes (6.9–12.7%) and Bacteroides (5.2–8.5%)** were the major genera. **Lactobacillus** and **Escherichia** were notably observed at D. – 3–D.3 (1.2%) and D. – 3–D.3 (0.2–0.4%), respectively. For AMR, a distinct cluster of AMR determinants was observed at D.8, mainly conferring resistance to macrolide–lincosamide–streptogramin (mefA), *β-lactam* (cfxA6 and aci1) and phenicol (rlmN).In contrast, at D.-3-D.3, a high abundance of determinants with aminoglycoside (AMG) (sat, aac(6)-aph(2"), aadA and acrF), *β-lactam* (fus-1, cepA and mrdA), multidrug resistance (MDR) (gadW, mdtE, emrA, evgS, toIC and mdtB), phenicol (catB4 and cmlA4), and sulfonamide patterns (sul3) was observed. Further, canonical correlation analysis (CCA) plot shows association of Escherichia coli with aac(6')-aph(2''), emrA, mdtB, catB4 and cmlA4 at D. – 3, D.0 and/or D.3 whereas at D.8 shows associations between Prevotella and mefA, cfxA6 and aci1.

Source: Gunnaporn Suriyaphol, Biochemistry Unit, Department Of Physiology, Faculty Of Veterinary Science, Chulalongkorn University, 39, Henri Dunant Road, Wangmai, Pathumwan, Bangkok, 10330, Thailand. Dynamics Of The Fecal Microbiome And Antimicrobial Resistome In Commercial Piglets During The Weaning Period. Sci Rep 11, 18091 (2021). https://doi.org/10.1038/s41598-021-97586-9

#### 7. Mechanisms Of Colonization Resistance Against Clostridioides Difficile

This review concludes that since antibiotic resistance is a prominent threat to today's society, there is an urgent need to develop innovative approaches for combatting antibiotic-resistant bacterial infections. Recent advances in technology have greatly improved the understanding of the dynamics between C difficile, the host, and the gut microbiota. Restoration of bile acids, SCFAs, or different consortia of commensals in the gut represents promising therapies that are currently being explored. Further, future advances in the rational and targeted design for delivery of these metabolites to the gut are needed to effectively restore colonization resistance against C difficile.

Source: Casey M Theriot, Department Of Population Health And Pathobiology, College Of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, USA. Mechanisms Of Colonization Resistance Against Clostridioides Difficile. The Journal of Infectious Diseases, Volume 223, Issue Supplement\_3, 15 June (2021), Pages S194–S200. <a href="https://doi.org/10.1093/infdis/jiaa408">https://doi.org/10.1093/infdis/jiaa408</a>

#### 8. The Gut Microbiome As A Reservoir For Antimicrobial Resistance

This review shows that how the gut acts as a reservoir for antimicrobial resistance, colonization resistance, and how disruption of the microbiome can lead to colonization by pathogenic organisms. There is a focus on the gut as a reservoir for  $\beta$ -lactam and plasmid-mediated quinolone resistance. Finally, the role of functional metagenomics and long-read sequencing technologies to detect and understand antimicrobial resistance genes within the gut microbiome is discussed, along with the potential for future microbiome-directed methods to detect and prevent infection.

Source: Jennie H Kwon, Department Of Medicine, Washington University School Of Medicine In St. Louis, St Louis, Missouri, USA. The Gut Microbiome As A Reservoir For Antimicrobial Resistance. The Journal of Infectious Diseases, Volume 223, Issue Supplement\_3, 15 June (2021), Pages S209–S213. https://doi.org/10.1093/infdis/jiaa497

# 9. Signal Versus Noise: How To Analyze The Microbiome And Make Progress On Antimicrobial Resistance

This review discussed the understanding of the risk from antimicrobial resistance organism (ARO) acquisition; the gut microbiome's ability to resist colonization with AROs; how experimental model systems can test these initial, global insights to arrive at more granular, mechanistic ones; and suggest a path forward to make further progress in the field.

Source: Krishna Rao, Department Of Internal Medicine, Division Of Infectious Diseases, University Of Michigan, Ann Arbor, Michigan, USA. Signal Versus Noise: How To Analyze The Microbiome And Make Progress On Antimicrobial Resistance. The Journal of Infectious Diseases, Volume 223, Issue Supplement\_3, 15 June (2021), Pages S214–S221. <u>https://doi.org/10.1093/infdis/jiab184</u>

# 10. Beyond Fecal Microbiota Transplantation: Developing Drugs from the Microbiome

The transfer of live gut microbes may transform patient care across a range of autoimmune, metabolic, hepatic, and infectious diseases. One early approach, fecal microbiota transplantation, has shown promise in *Clostridiodes difficile* infection and the potential for improving clinical and public health outcomes for other antibiotic-resistant bacteria. Further, these clinical successes have motivated the development of microbiome drugs, which will need to address challenges in safety, uniformity, and delivery while seeking to preserve the benefits of using whole microbiome communities as novel therapeutics and an innovative platform for drug discovery.

Source: Zain Kassam, Finch Therapeutics, Somerville, Massachusetts, USA. Beyond Fecal Microbiota Transplantation: Developing Drugs from the Microbiome. The Journal of Infectious Diseases, Volume 223, Issue Supplement\_3, 15 June (2021), Pages S276–S282. <a href="https://doi.org/10.1093/infdis/jiaa700">https://doi.org/10.1093/infdis/jiaa700</a>

#### 11. A Global Metagenomic Map Of Urban Microbiomes And Antimicrobial Resistance

This review present a global atlas of 4,728 metagenomic samples from mass-transit systems in 60 cities over 3 years, representing the first systematic, worldwide catalog of the urban microbial ecosystem. This atlas provides an annotated, geospatial profile of microbial strains, functional characteristics, antimicrobial resistance (AMR) markers, and genetic elements, including 10,928 viruses, 1,302 bacteria, 2 archaea, and 838,532 CRISPR arrays not found in reference databases.

Scientists have identified 4,246 known species of urban microorganisms and a consistent set of 31 species found in 97% of samples that were distinct from human commensal organisms. Profiles of AMR genes varied widely in type and density across cities. Cities showed distinct microbial taxonomic signatures that were driven by climate and geographic differences. Further, these results constitute a high-resolution global metagenomic atlas that enables discovery of organisms and genes, highlights potential public health and forensic applications, and provides a culture-independent view of AMR burden in cities.

Source: Christopher E. Mason, Weill Cornell Medicine; The Bin Talal Bin Abdulaziz Alsaud Institute For Computational Biomedicineand The Worldquant Initiative For Quantitative Prediction, Weill Cornell Medicine, New York, USA. A Global Metagenomic Map Of Urban Microbiomes And Antimicrobial Resistance. Journal Cell, Volume 184, Issue 13, 24 June (2021), Pages 3376-3393.e17. https://doi.org/10.1016/j.cell.2021.05.002

#### 12. Impact Of Antibiotic Resistance Genes In Gut Microbiome Of Patients With Cirrhosis

The aims of the study was to determine the impact of antibiotic resistance genes (ARGs) in cirrhosis-related gut metagenome on outcomes and disease progression, study the effect of rifaximin on ARG burden, and compare ARGs in cirrhosis with chronic kidney disease (CKD) and diabetes.

Researchers have concluded that Cirrhosis is associated with high gut microbial ARG gene burden compared with controls, which worsens with disease progression and may be different from chronic kidney disease (CKD) and diabetes. ARGs are not affected by rifaximin and are associated with hospitalizations and death.

Source: Jasmohan S. Bajaj, Division Of Gastroenterology, Hepatology And Nutrition, Virginia Commonwealth University And Central Virginia Veterans Healthcare System, 1201 Broad Rock Boulevard, Richmond, Virginia. Impact Of Antibiotic Resistance Genes In Gut Microbiome Of Patients With Cirrhosis. Journal Gastroenterology, Volume 161, Issue 2, P508-521.E7, August 01, (2021). <u>https://doi.org/10.1053/j.gastro.2021.04.013</u>

# 13. Biology And Applications Of Co-Produced, Synergistic Antimicrobials From Environmental Bacteria

Environmental bacteria, such as Streptomyces spp., produce specialized metabolites that are potent antibiotics and therapeutics. Selected specialized antimicrobials are co-produced and function together synergistically. Co-produced antimicrobials comprise multiple chemical classes and are produced by a wide variety of bacteria in different environmental niches, suggesting that their combined functions are ecologically important.

This study highlights the exquisite mechanisms that underlie the simultaneous production and functional synergy of 16 sets of co-produced antimicrobials. Further, they have also proposed methods to target co-produced antimicrobials which could widen the scope and applications.

Source: Justin R. Nodwell, Department Of Biochemistry, Temerty Faculty Of Medicine, University Of Toronto, Toronto, Ontario, Canada. Biology And Applications Of Co-Produced, Synergistic Antimicrobials From Environmental Bacteria. Nat Microbiol 6, 1118–1128 (2021). https://doi.org/10.1038/s41564-021-00952-6

# 14. An Omics-Based Framework For Assessing The Health Risk Of Antimicrobial Resistance Genes

Researchers have developed an 'omics-based' framework to evaluate antimicrobial resistance genes (ARG) risk considering human-associatedenrichment, gene mobility, and host pathogenicity.

This framework classifies human-associated, mobile ARGs (3.6% of all ARGs) as the highest risk, which further differentiate as 'current threats' (Rank I; 3%) already present among pathogens and 'future threats' (Rank II; 0.6%) novel resistance emerging from non-pathogens. This framework identifies 73 'current threat' ARG families. Out of 73, 35 were among the high-risk ARGs proposed by the World Health Organization and other literature; the remaining 38 were significantly enriched in hospital plasmids. By evaluating all pathogen genomes since framework construction, scientists have also confirmed ARGs that recently transferred into pathogens which were significantly enriched in Rank II ('future threats'). Lastly, applied the framework to gut microbiome genomes from fecal microbiota transplantation donors. Researchers have found that although ARGs were widespread (73% of genomes), only 8.9% of genomes contained high-risk ARGs. Further, this framework provides an easy-to-implement approach to identify current and future antimicrobial resistance threats, with potential clinical applications including reducing risk of microbiome-based interventions.

Source: Tong Zhang, Environmental Microbiome Engineering And Biotechnology Laboratory, Department Of Civil Engineering; School Of Public Health And Center For Environmental Engineering Research, The University Of Hong Kong, Hong Kong SAR, China. An Omics-Based Framework For Assessing The Health Risk Of Antimicrobial Resistance Genes. Nat Commun 12, 4765 (2021). <u>https://doi.org/10.1038/s41467-021-25096-3</u>

# 15. Drivers Of Global Media Attention And Representations For Antimicrobial Resistance Risk: An Analysis Of Online English And Chinese News Media Data, 2015–2018

This study examined online news media attention for antimicrobial resistance (AMR) risk and analyzed how AMR risk was communicated using a global sample of English and Chinese news articles.

The content analysis found that (1) heterogeneous medical terminologies and the 'superbug' frame were most commonly used to define AMR or AMR risk; (2) a temporal increase in communicating microbial evolution as a process of AMR was identified but communication about inappropriate AMU in general consumers as the cause of AMR remained inadequate; and (3) the multifaceted consequences of AMR and individual actions that can be taken to tackle AMR were inadequately communicated.

Source: Qiuyan Liao, School Of Public Health, Li Ka Shing Faculty Of Medicine, The University Of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong, China. Drivers Of Global Media Attention And Representations For Antimicrobial Resistance Risk: An Analysis Of Online English And Chinese News Media Data, 2015–2018. Antimicrob Resist Infect Control 10, 152 (2021). https://doi.org/10.1186/s13756-021-01015-5

# 16. Knowledge, Attitudes And Behaviors On Antibiotic Use And Resistance Among Healthcare Workers In Italy, 2019: Investigation By A Clustering Method

The aim of this study was to compare knowledge, attitudes and behaviors on antibiotic use and resistance across different groups of Italian healthcare workers (HCW).

This study concluded that Italian HCW exhibited different knowledge, attitudes, and behaviors on antibiotic use and resistance. These findings raised the need for educational and training interventions targeting specific professional groups.

Source: Michela Sabbatucci, Department Infectious Diseases, Italian National Institute Of Health And Directorate General Health Prevention, Communicable Diseases And International Prophylaxis, Ministry Of Health, Rome, Italy. Knowledge, Attitudes And Behaviors On Antibiotic Use And Resistance Among Healthcare Workers In Italy, 2019: Investigation By A Clustering Method.Antimicrob Resist Infect Control 10, 134 (2021). <u>https://doi.org/10.1186/s13756-021-01002-w</u>

# 17. Increasing Incidence And Antimicrobial Resistance In Escherichia Coli Bloodstream Infections: A Multinational Population-Based Cohort Study

This study determines factors associated with E. coli Bloodstream Infections (BSI) incidence rate and third-generation cephalosporin resistance in a multinational population-based cohort.

Researchers concluded that increases in overall and third-generation cephalosporin-resistant standardized E. coli BSI rates were clinically important. Overall, E. coli BSI incidence rates were 40–104% greater than previous investigations from the same study areas. Region, sex, and age are important variables when analyzing E. coli BSI rates and third-generation cephalosporin resistance in E. coli BSIs. Considering E. coli is the most common cause of BSIs, this increasing burden and evolving third-generation cephalosporin resistance will have an important impact on human health, especially in aging populations.

Source: Melissa C. Mackinnon, Department Of Population Medicine, University Of Guelph, 50 Stone Rd E, Guelph, Canada. Increasing Incidence And Antimicrobial Resistance In Escherichia Coli Bloodstream Infections: A Multinational Population-Based Cohort Study. Antimicrob Resist Infect Control 10, 131 (2021). https://doi.org/10.1186/s13756-021-00999-4

# 18. Animal Source Food Eating Habits Of Outpatients With Antimicrobial Resistance In Bukavu, D.R. Congo

The objective of the study was to evaluate the eating habits of animal source food (ASF) by outpatients with antimicrobial resistance through an analysis of (i) the association of their antimicrobial resistance with animal source food (ASF) consumption; (ii) the influence of the types of ASF on their antimicrobial resistance.

The findings of this study suggest a contribution of human nutrition to antimicrobial resistance frequency. Study results show the existence of a high prevalence of multi-drug resistant bacteria in patients for whom eating beef, pork and drinking milk are major risk factors. Therefore, a stricter control of antibiotic usage in livestock production and of their presence in ASF is recommended.

Source: Olivier Basole Kashongwe, Institut Supérieur Des Techniques Médicales (ISTM) De Bukavu, B.P. 3036, Bukavu, Democratic Republic Of Congo; Livestock Production Systems Group, Department Of Animal Sciences, Egerton University, Box 536-20115, Njoro, Kenya And Leibniz Institute For Agricultural Engineering And Bioeconomy (ATB), Max-Eyth-Allee 100, 14469, Potsdam, Germany. Animal Source Food Eating Habits Of Outpatients With Antimicrobial Resistance In Bukavu, D.R. Congo. Antimicrob Resist Infect Control 10, 124 (2021). https://doi.org/10.1186/s13756-021-00991-y

# 19. Effects Of Kefir On Doxorubicin-Induced Multidrug Resistance In Human Colorectal Cancer Cells

Kefir, an acidic-alcoholic fermented milk product, is known to be associated with reduced cancer incidence. Multidrug resistance (MDR) against chemotherapeutic agents frequently occurs in cancer cells, leading to cancer therapy failure. This study explores the potential chemo-sensitizing effects of kefir (i.e., kefir supernatant).

Study results demonstrated that cells treated with kefir attenuated MDR and improved the anticancer effect of DOX in drug-resistant cells. Kefir increased intracellular accumulation of ROS and DOX in drug-resistant cells. Kefir decreased the gene and protein expressions of adenosine triphosphate binding cassette (ABC) transporters, a drug efflux pump, in drug-resistant cells. Upstream regulators of ABC transporters, such as ERK 1/2, JNK and NF-kB were also modulated by kefir.

Study data suggest that kefir consumption may be helpful in patients receiving DOX chemotherapy owing to its chemo-sensitizing effects.

Source: Sung Gu Han, Department Of Food Science And Biotechnology Of Animal Resources, Konkuk University, Seoul 05029, Republic Of Korea. Effects Of Kefir On Doxorubicin-Induced Multidrug Resistance In Human Colorectal Cancer Cells. Journal of Functional Foods, Volume 78, March (2021), 104371. https://doi.org/10.1016/j.jff.2021.104371

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