(20)

交叉前沿：探索微生物和免疫學對泌尿系統健康與治療的影響

Intersecting Frontiers: Exploring Microbial & Immunological Influences in Urological Health & Therapeutics

時　　間：113 年 6 月 22 日(星期六) 13:30~17:30
地　　點：臺北榮民總醫院 致德樓第十會議室

13:30-13:35	***Opening Remarks***	黃志賢教授 William JS Huang
	座長：阮雍順　教授 (Yung-Shun Juan)	
13:35-14:00	探討尿液中微生物群與泌尿系統疾病之間的關聯 Exploring the Association Between Gut and Urine Microbiota and Prostate Disease	李香瑩醫師 Hsiang-Ying Lee
	座長：黃志賢 教授 (William JS Huang)	
14:00-14:15	無精症患者腸道與睪丸的微生物特徵 Distinctive Features of Gut Microbiota in Azoospermic Men	黃奕燊醫師 I-Shen Huang
14:15-14:30	微生物體在腎草酸鈣結石形成中所扮演的角色 Role of Microbiome in Kidney Calcium Oxalate Stone Formation	陳威任醫師 Wei-Ren Chen
14:30-14:40	Discussion	
	座長：林子平 主任 (Tzu-Ping Lin)	
14:40-15:05	泌尿道感染：細菌與宿主特性、抗藥性與反覆性感染 Urinary Tract Infections: Bacteria and Host Characteristics, Antibiotic Resistance, and Recurrent Infections	高正彥副教授 Cheng-Yen Kao
15:05-15:20	以泌尿道感染之尿液培養研究多重菌株的交互作用與致病機轉 Investigation of Bacterial Interplay Between Strains and Bacterial Pathogenesis in Polymicrobial Urinary Tract Infections	林志杰醫師 Chih-Chieh Lin
15:20-15:35	反覆性泌尿道感染的宿主特徵 Host Characteristics Associated with Recurrent Urinary Tract Infection	范玉華醫師 Yu-Hua Fan
15:35-15:45	Discussion	
15:45-16:00	***Coffee Break***	

座長：鍾孝仁 主任 (Hsiao-Jen Chung)

16:00-16:20	抗體藥物複合藥及免疫檢查點抑制劑在轉移性泌尿上皮癌之突破 New Breakthrough with ADC and CPI in Metastatic Urothelial Carcinoma	賴峻毅醫師 Jiun-I Lai
16:20-16:40	腎細胞癌手術輔助治療的突破 Breakthrough of Adjuvant Therapy in Renal Cell Carcinoma	黃子豪醫師 Tzu-Hao Huang

座長：黃逸修 主任 (Yi-Hsiu Huang)

16:40-17:00	免疫療法在攝護腺癌中的進展 Immunotherapy in Prostate Cancer	蔡承翰醫師 Cheng-Han Tsai
17:00-17:15	Discussion	
17:15-17:20	***Closing Remarks***	黃志賢教授 William JS Huang

Exploring the association between gut and urine microbiota and prostate disease

探討尿液中微生物群與泌尿系統疾病之間的關聯

Hsiang-ying lee

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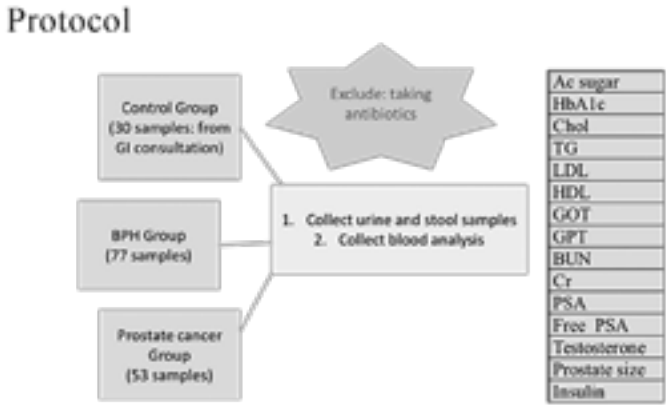
Background

Crosstalk between an organism and its gut commensal microbiota

Gastrointestinal microbiota

Indirect interactions such as regulation of the immune system, metabolism changes, and impacts on therapy(Influence on the cancer immune microenvironment, Influence in treatment response to agents, Chemotherapy and immunotherapy, Microbiota-driven tumorigenesis , From a state of microbial balance to a state of dysbiosis, Activation of Toll-like receptors, Genomic instability and DNA damage in host cells)



Results → Urine samples

(Stool samples are not significant difference)

Comparisons of demographic, clinical characteristics and bacteria alpha diversity

Correlation analysis:Positive correlation between bacteria and IPSS

Correlation analysis:Positive correlation between bacteria and IPSS subgroup

Conclusions

Significant difference of urine microbiota between control and stone diseases groups

Future: urine metabolites and microbiota

Stone culture to exclude infection stone ?

Distinctive features of gut microbiota in azoospermic men

無精症患者腸道與睪丸的微生物特徵

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Background: Despite previous research revealing taxonomic disparities between the microbiomes of infertile men and healthy fertile controls, there remains limited understanding of the gastrointestinal microbiota's role in the development of male infertility. Our study focuses on elucidating the potential link between gut microbiota and defective spermatogenesis, particularly in the context of non-obstructive azoospermia (NOA) and obstructive azoospermia (OA). We aim to investigate correlations and identify pathogenic taxonomic units using stool samples obtained from individuals diagnosed with these conditions.

Methods: Stool samples were collected prospectively from 33 azoospermic men, consisting of 21 individuals diagnosed with NOA and 12 individuals diagnosed with obstructive azoospermia OA. The composition of the gut microbiome was assessed using a 16S rRNA gene-based sequencing protocol.

Results: Men diagnosed with NOA exhibited increased α diversity compared to OA counterparts. However, the composition of the microbiome (beta diversity) in NOA closely resembled that of the OA gut microbiome. Analysis at the phylum level revealed Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria as the dominant phyla, collectively accounting for 98.1% in the OA group and 98.2% in the NOA group. Predominant genera identified in OA included Phocaeicola, Mediteraneibacter, Escherichia-Shigella, Blautia, and Faecalibacillus, while those in NOA were Phocaeicola, Escherichia-Shigella, Mediteraneibacter, Bacteroides, and Bifidobacterium, respectively.

Conclusion: Our study investigated the gut microbiome composition in men diagnosed with OA and NOA, offering potential insights for novel treatments targeting defective spermatogenesis and aiding in its diagnosis.

Role of microbiome in kidney calcium oxalate stone formation

微生物相在含鈣腎臟結石形成的角色

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Calcium oxalate crystals, the predominant composition in kidney stones, arises from the oversaturation of calcium and oxalate ions in urine. Traditionally, high intake of oxalate-rich foods, imbalanced calcium consumption, impaired intestinal oxalate transport, and gastrointestinal malabsorption (e.g., post-gastric bypass surgery) were regarded as factors which can elevate oxalate absorption, consequently elevating urinary oxalate levels and the risk of kidney stone disease. The gastrointestinal microbiome, particularly enriched with oxalate-degrading bacteria, plays a crucial role in reducing oxalate absorption and urinary oxalate concentration by influencing the expression of oxalate transporters and net intestinal oxalate transport, leading to lower renal stone disease risk.

Traditionally, urinary tract was considered a sterile environment. However, using microbiota analysis methodology, studies suggest that urinary tract owns its unique microbiota, and is very different from gut microbiota. Recent studies also revealed the possible impact of the urinary microbiome in renal stone formation. In this mini-review, we reviewed recent evidence between the mechanism between urine microbiome and renal stone formation.

Urinary tract infections: Bacteria and host characteristics, antibiotic resistance, and recurrent infections

泌尿道感染：細菌與宿主特性、抗藥性與反覆性感染

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The issue of antimicrobial resistance and recurrent urinary tract infections (UTIs) remains a critical concern in clinical practice. In our previous research, we conducted a comparative analysis of *Escherichia coli* strains isolated from urinary samples collected during two time periods, 2009-2010 and 2020, revealing variations in bacterial characteristics. Furthermore, we identified a direct association between the characteristics of *E. coli* strains and the attributes of the host. Specifically, our observations indicated that *E. coli* strains isolated from elderly individuals exhibited heightened resistance to antimicrobial agents and fewer virulence factors. Notably, a significant proportion (77.4%) of strains isolated from the 0 to 3 age group belonged to phylogenetic group B2. Antimicrobial susceptibility testing revealed a notable escalation in resistance among *E. coli* strains with advancing host age, with phylogenetic group B2 isolates displaying higher susceptibility to antimicrobial agents compared to isolates from phylogenetic groups A, B1, and D.

In our investigation aimed at assessing plasmid-mediated quinolone resistance (PMQR) in fluoroquinolone non-susceptible *E. coli* (FQNSEC) isolated from patients with UTIs, we observed a substantial prevalence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) *E. coli* among FQNSEC isolates. Additionally, we found that plasmids carrying the *qnr* gene exhibited high transferability, resulting in resistance to other classes of antimicrobials in the transconjugants. Through genome characterization of XDR-*E. coli* strain EC1390, we identified two plasmids that contributed to antimicrobial resistance, bacterial growth in nutrition-limited environments, biofilm formation, and cell adhesion.

Furthermore, our findings indicated that uropathogens in recurrent UTIs exhibited greater virulence in genetically closely related *E. coli* strains. The heightened bacterial virulence observed in the younger age group (<20 years) and in patients without anatomical/functional defects or immune dysfunction suggests that virulent uropathogenic *E. coli* strains play a crucial role in the development of recurrent UTIs in otherwise healthy individuals. Additionally, prior antibiotic therapy, particularly fluoroquinolones administered within three months, could induce subsequent antimicrobial resistance in genetically closely related *E. coli* strains, thereby contributing to recurrent UTIs.

Investigation of bacterial interplay between strains and bacterial pathogenesis in polymicrobial urinary tract infections

以泌尿道感染之尿液培養研究多重菌株的交互作用與致病機轉

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Background and Objectives: Urinary tract infection is the most common bacterial infection globally, making it a significant public health concern. While cases caused by Escherichia coli are the most prevalent, other strains such as Staphylococcus belonging to Gram-positive cocci and Enterococcus species are also opportunistic pathogens in urinary tract infections. However, the current understanding of the mechanism behind polymicrobial urinary tract infections remains unclear.

Methods and Processes: In this study, we collected forty-four sets of samples to explore the relationship between patients, polymicrobial pathogens, and the disease. To assess bacterial pathogenicity, we employed a model using wax moth larvae to simulate in vivo infection experiments. This allowed us to evaluate the differences in virulence between single bacterial strains and various combinations of two strains. Additionally, we examined the growth patterns using liquid culture media outside the host, observing whether the two strains mutually promoted replication or inhibited each other's growth. Furthermore, we investigated the expression of virulence factors related to urinary tract infections, such as the ability to synthesize biofilms. For example, we stained biofilms adhering to the bottom of a 96-well plate with 1% crystal violet solution after washing with phosphate-buffered saline and fixing with methanol. The quantification of growth was then performed by reading the absorbance values after dissolution in 95% ethanol.

Research Findings: Among the forty-four collected sample sets, the combination of Escherichia coli with Enterococcus faecalis was the most prevalent (13.64%), followed by combinations of E. coli with Klebsiella pneumoniae (9.09%) and E. coli with Pseudomonas aeruginosa and E. coli with Streptococcus agalactiae (6.82%).

Through the in vivo infection model with live animals, we identified five sets (Patients #4, #11, #16, #18, #24) where the strains displayed higher toxicity when co-cultured than when cultured alone. Conversely, another set (Patient #3) showed the opposite phenomenon. Subsequent experiments on the phenotypes will focus on the strains from these six sets with significant differences in toxicity.

In Patient #4, when culturing pathogenic bacteria in tryptic soy broth (TSB), the quantity of Enterobacter hormaechei significantly decreased when co-cultured with Staphylococcus aureus. Growth conditions for S. aureus were found to be inferior when cultured in mixed healthy human urine compared to TSB.

Regarding biofilm synthesis, significant differences in biofilm formation were observed on the second and third days for strains from Patients #3 and #4 when cultured alone or together. Patients #11, #18, and #24 exhibited significant differences on the first day, while Patient #16 did not show any significant differences.

Host characteristics associated with recurrent urinary tract infection

反覆性泌尿道感染的宿主特徵

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Recurrent urinary tract infection (UTI) stands out as a prevalent issue in urological clinics. Recent studies have unveiled new insights into recurrent UTI, positioning it as a distinct entity separate from the initial infection. The pathogenesis of recurrent UTI appears to involve two primary mechanisms: bacterial factors and deficiencies in host defense.

Among bacterial factors, the survival of bacteria in the urinary bladder post-antibiotic treatment and the subsequent development of intracellular bacterial communities emerge as pivotal contributors. Host defense deficiency, marked by impaired pathogen recognition and compromised urothelial barrier function, assumes a crucial role in this recurrence.

Essential risk factors for recurrent UTI encompass immunodeficiency and anatomical abnormalities in the urogenital tract. In otherwise healthy women, voiding dysfunction and behavioral factors contribute to an increased risk of recurrent UTI. Notably, factors such as sexual intercourse and estrogen deficiency in postmenopausal women exhibit the strongest associations with recurrent UTI.

Clinical evidence suggests that serum macrophage colony-stimulating factor and urinary nerve growth factor hold promise as potential predictive biomarkers for recurrent UTI. Efficacy in preventing UTI has been demonstrated in clinical trials for the oral immunoactive agent OM-89. Additionally, the latest guidelines endorse vaccines as a recommended preventive measure for recurrent UTI.

New breakthrough with ADC and CPI in metastatic urothelial carcinoma

抗體藥物複合藥及免疫檢查點抑制劑在轉移性泌尿上皮癌之突破

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Metastatic urothelial carcinoma is a deadly disease with poor prognosis. For decades, the standard of care first line treatment is chemotherapy, and the 5-year overall survival is less than 10%. Many efforts have been made to develop novel agents and treatment for this disease, but until recently, most regimens have not been superior to conventional chemotherapy.

In the past few years, there has been a wave of breakthrough in this disease setting. The ADCs include enfortumab vedotin, Sacituzumab govetecan have shown great efficacy in this setting. Checkpoint inhibitors have also proven effective in the second line setting. Although the combination of checkpoint inhibitors to chemotherapy in first line have previously been unsuccessful, in 2023 two phase III clinical trials that combined checkpoint inhibitors to chemotherapy and checkpoint inhibitors to ADC have shown great efficacy in the 1st line setting. This has marked a new era in the treatment algorithm in the field of metastatic urothelial carcinoma.

In my presentation, I will review the novel breakthroughs regarding checkpoint inhibitors and ADC in metastatic urothelial carcinoma. I will discuss treatment concepts and algorithms for treatment planning in this disease setting, and provide a through review of the current state of art medical systemic treatment for metastatic urothelial carcinoma.

Breakthrough of adjuvant therapy in renal cell carcinoma

腎細胞癌手術輔助治療的突破

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Adjuvant therapy after surgical resection for high risk renal cell carcinoma had been proposed in recent decades, while no definitive benefit has been established. Various tyrosine kinase inhibitors (TKIs) have been evaluated in clinical trials and only S-TRAC trial demonstrated a tangible progression-free-survival benefit.

The emergence of immunotherapy has brought great success in treating advanced renal cell carcinoma, and has spurred numerous trials aimed at expanding the adjuvant treatment landscape. Based on KEYNOTE-564 trial, pembrolizumab stands as the only medication that shows the overall survival benefit, whereas other immunotherapy agents could not reach improvement in the adjuvant scenario. Notably, there is no universally accepted model for estimating the risk of recurrence after nephrectomy, resulting in highly heterogeneous patient inclusion across trials. Meanwhile, research endeavors targeting histopathological features or biomarkers to identify high risk population are also ongoing.

Additionally, caution is warranted in interpreting the results of adjuvant therapy, given its fundamental disparity from treatments for advanced or metastatic diseases. Quality of life is another critical factor to consider in the context of adjuvant treatment. Thus, despite the promising outcome of KEYNOTE-564, the importance of appropriate patient selection remains paramount. Currently, many trials are actively underway, fostering hope for further advancements in this field.