DEVELOPMENT OF A MICROPHYSIOLOGICAL MODEL OF CATHETER-ASSOCIATED URINARY TRACT INFECTION

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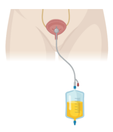
Clinical relevance



Urinary catheters are the most commonly used indwelling medical devices and Catheter-Associated Urinary Tract Infections (CAUTIs) are among the leading causes of nosocomial infections. They occur in about 13000 patients and cost 130 million CHF annually in Switzerland alone. Moreover, the increasing antibiotic resistance makes it progressively harder to treat.

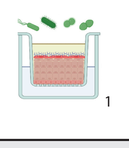
Catheterization alters urination dynamics. It also creates a constant inflamation of the urinary tract tissue which in response releases material on the catheter and urothelium. This particular physicochemical environment promotes pathogen adhesion, biofilm formation, colonization of the urinary tract and antibiotic resistance.
Yet, it is unclear which factors and mechanisms create this favorable niche.

How to study CAUTI?

Despite a significant amount of clinical research, the current methods for investigating the mechanisms of CAUTI and evaluating different catheter materials and treatments are limited.

Although *in vivo* models of CAUTI provide responses at the organism scale, they raise ethical concerns, lack the experimental power of *in vitro* approaches and present key structural and physiological differences with human tissues.

In contrast, fluidic systems have been developed to mimic catheterized urinary tracts by using vessels and culturing pathogens within them. Yet, they don't incorporate any mammalian cells, which is essential for reproducing the interactions between the host tissue, pathogens, and the catheter, which are inherent to the complexity of CAUTI.



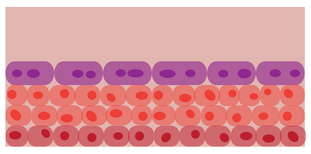
Finally, the recent development of *in vitro* bladder microtissue models for urinary tract infections is promising but most of them are currently not compatible with long-term bacterial infections or high-resolution timelapse imaging. They also can't incorporate a catheter and recapitulate the flow dynamics and tissue stretching due to micturition.

[1]

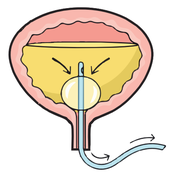
GOAL: Develop a microphysiological model of CAUTI by growing a human bladder urothelium in a microfluidic device before catheterizing it with a microtube and infecting it with uropathogens

Specifications of the model

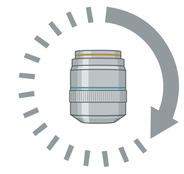
- Present a stratified urothelium from human cells



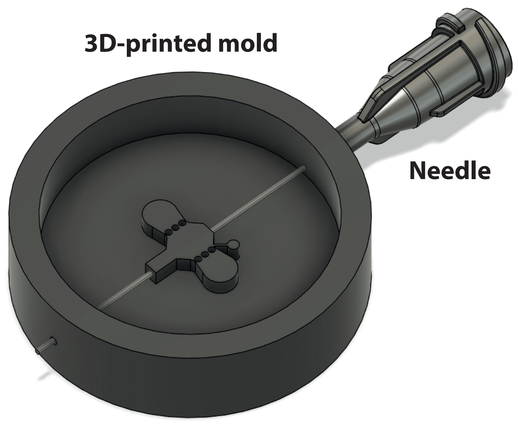
- Have an accessible lumen for flow perfusion and catheterization



- Be compatible with high-mag timelapse microscopy

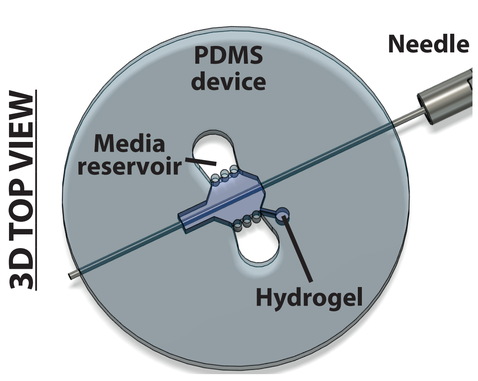


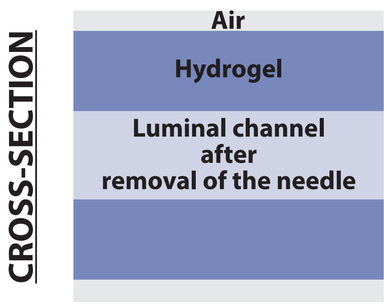
AIM 1: Generate a perfusable urothelium capable of hosting a catheter



Using a 3D printed mold and a 250-600µm needle, we generated a PDMS device with a lateral channel crossing a central chamber flanked by two reservoirs for nutritive media.

Actual 3D-printed mold *Actual microfluidic device*





Using the same needle, we shaped a lumen in hydrogel by polymerization type-I collagen in the central chamber, before pulling the needle out from the device.

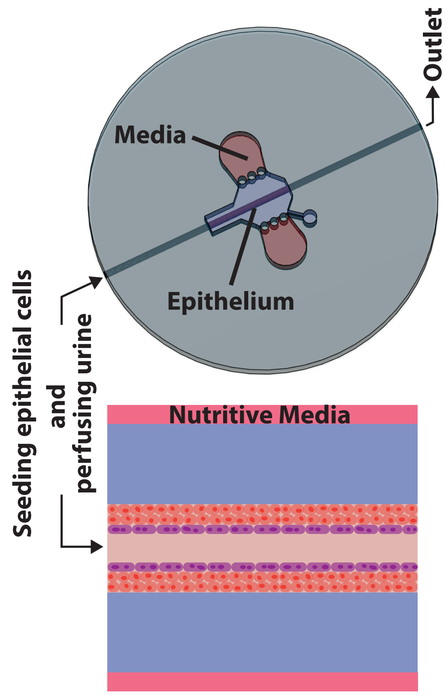
Video of the process

Seeding of human bladder epithelial cells into the lumen is expected to form a cylindric epithelium[2]. Further perfusion of synthetic urine media from its apical side should further promote its differentiation and stratification[2].

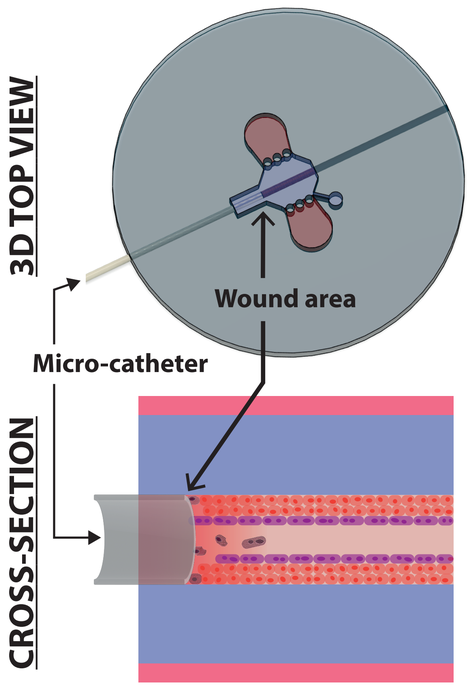
Characterization of the tissue
Confocal microscopy to measure the epithelium thickness.

Immunofluorescence to observe assess the differenciation into the different cell types.

Trans-Epithelial Electrical Resistance (TEER) to assess barrier strength.



AIM 2: Catheterize the lumen



Once the urothelium has matured, we will introduce a catheter-like microtube into the luminal channel until it reaches the tissue and creates a wound.
The material of the microtube will mimic that used for clinical catheters (silicon or PTFE).

We will perfom woundless catheterization as a control.

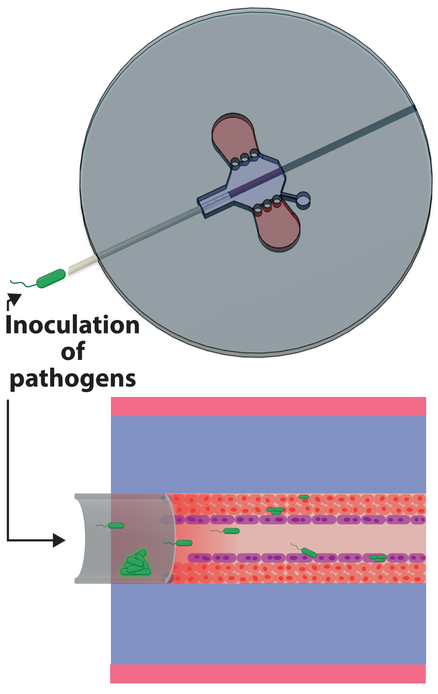
Characterization of the tissue-damage
Same as in Aim 1 and

Immunofluorescence and ELISA to measure the levels of fibrinogen and epithelial-secreted cytokines such as CXCL1 in the vicinity of the wound, on the surface of the catheter, and in the effluent media.

Timelapse to monitor cell shedding.

AIM 3: Infect the catheterized lumen with uropathogens

Following catheterization, we will introduce different uropathogens, starting with two common species, *E. coli* (CFT073 isolate) and *E. faecalis* (OG1RF isolate), directly through the catheter.



Characterization of the infection
Same as in Aim 1 and

Use timelapse confocal microscopy with fluorescently tagged strains to monitor bacterial colonization.

Crystal violet staining, immunostaining and omics to measure biofilm formation on the catheter.

Can we recapitulate biofilm formation and Intracellular Bacterial Communities[3]?

QUESTIONS

Are flow, tissue stretching, and micturition dynamics affecting urothelium development?

How catheterization increases colonization and biofilm formation? Through wounding, secretion of host material, or altered micturition dynamics?

Can we use this model to study polymicrobial infections? To test preventive and curative treatments and catheter materials?

In a hurry? Scan me!

REFERENCES

[1]*Adapted from* Flores, C. et al. A human urothelial microtissue model reveals shared colonization and survival strategies between uropathogens and commensals. Sci. Adv. 9, eadi9834 (2023).
[2]Paduthol, G et al., Poster #35: Human bladder microtissue model to study chronic and recurrent UTIs
[3]Sharma, K. et al. Dynamic persistence of UPEC intracellular bacterial communities in a human bladder-chip model of urinary tract infection. eLife 10, e66481 (2021).