

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

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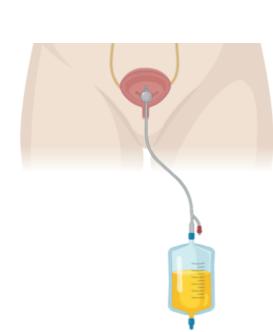
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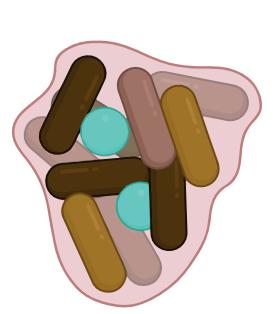
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Clinical relevance



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.



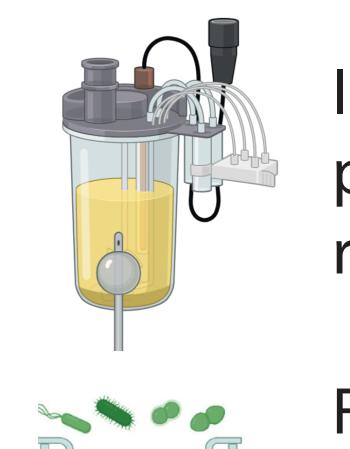
Catheterization alters urination dynamics. It also creates a constant inflammation of the urinary tract tissue which in response releases material on the catheter and urothelium. This particular physicochemical environment promotes pathogen adhesion, biofilm formation, colonization of the urinary tract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

How to study CAUTI?

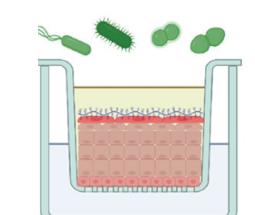
Despite a significant amount of clinical research, the current methods for investigating the mechanisms of CAUTI and evaluating different catheter materials and treatments are limited.



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.



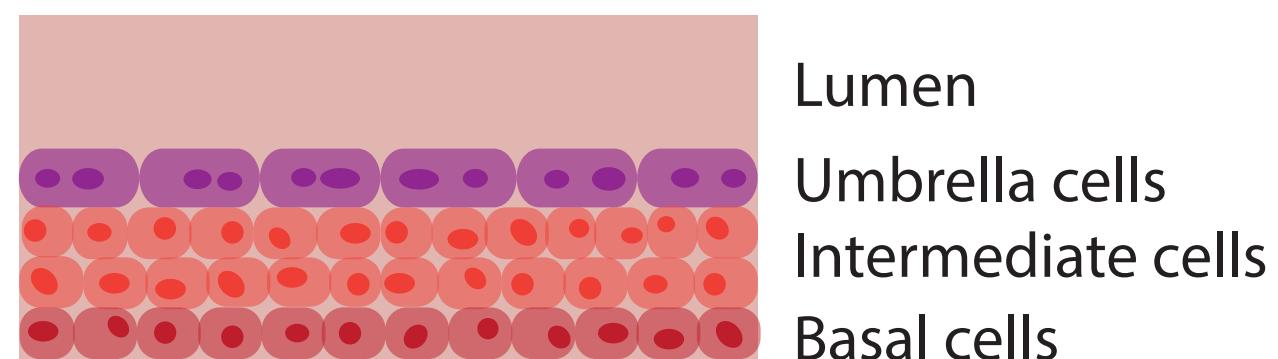
Finally, the recent development of *in vitro* bladder microtissue models for urinary tract infections is promising but most of them are currently not compatible with long-term bacterial infections or high-resolution timelapse imaging. They also can't incorporate a catheter and recapitulate the flow dynamics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

How does catheterization modify the microenvironment of the urinary tract to promote bacterial colonization?

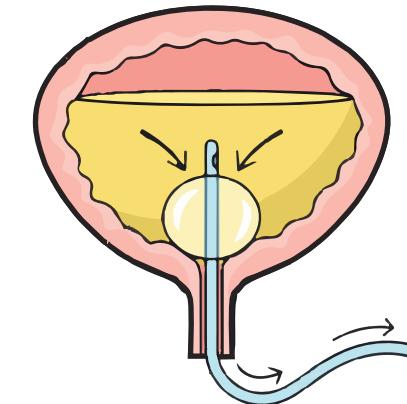
GOAL: Develop a microphysiological model of CAUTI by growing a human bladder urothelium in a microfluidic device before catheterizing it with a microtube and infecting it with uropathogens

Specifications of the model

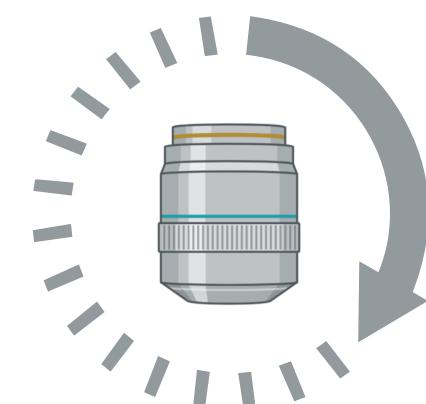
• Present a stratified urothelium from human cells



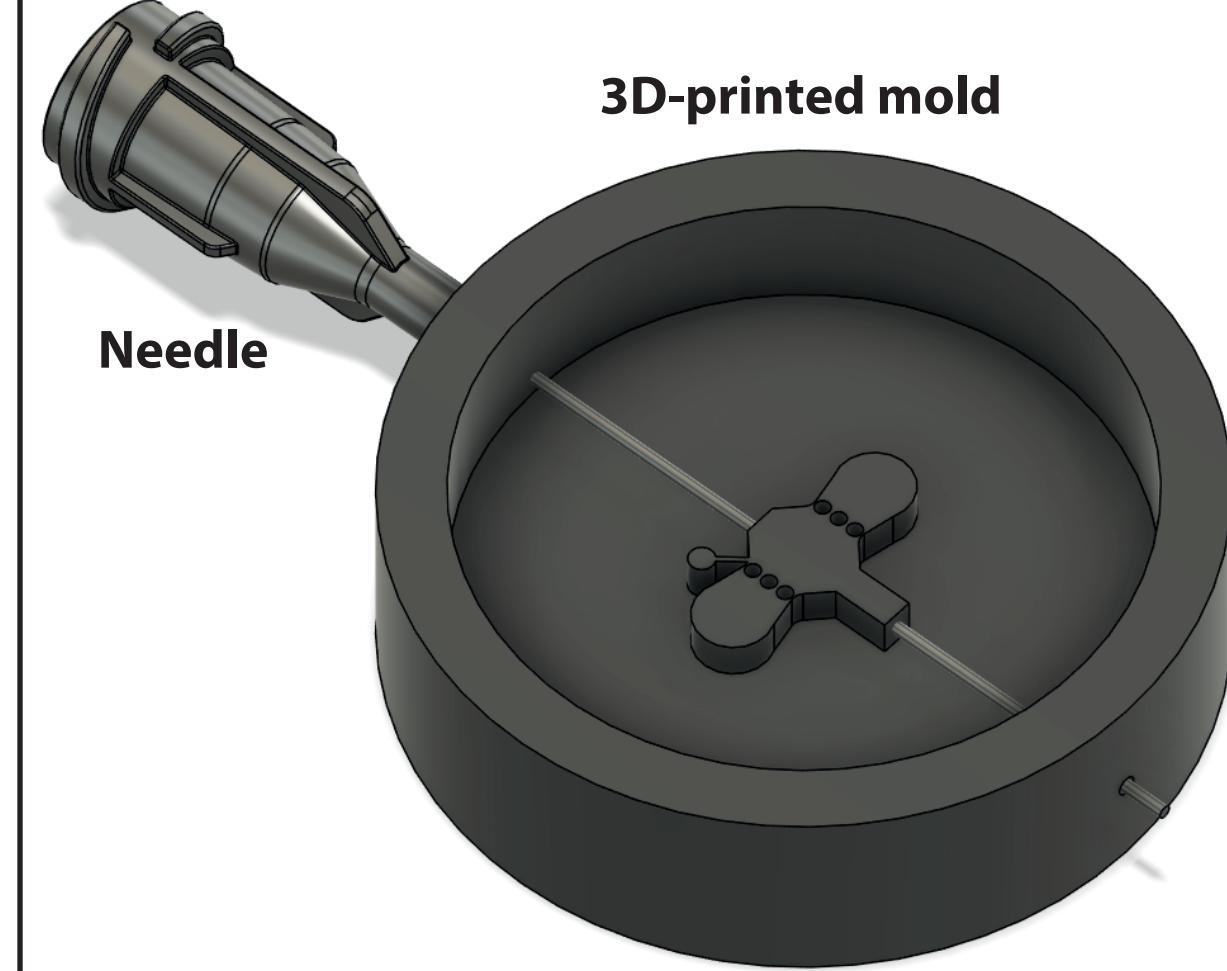
• Have an accessible lumen for flow perfusion, stretching, and catheterization



• Be compatible with high-mag timelapse microscopy



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

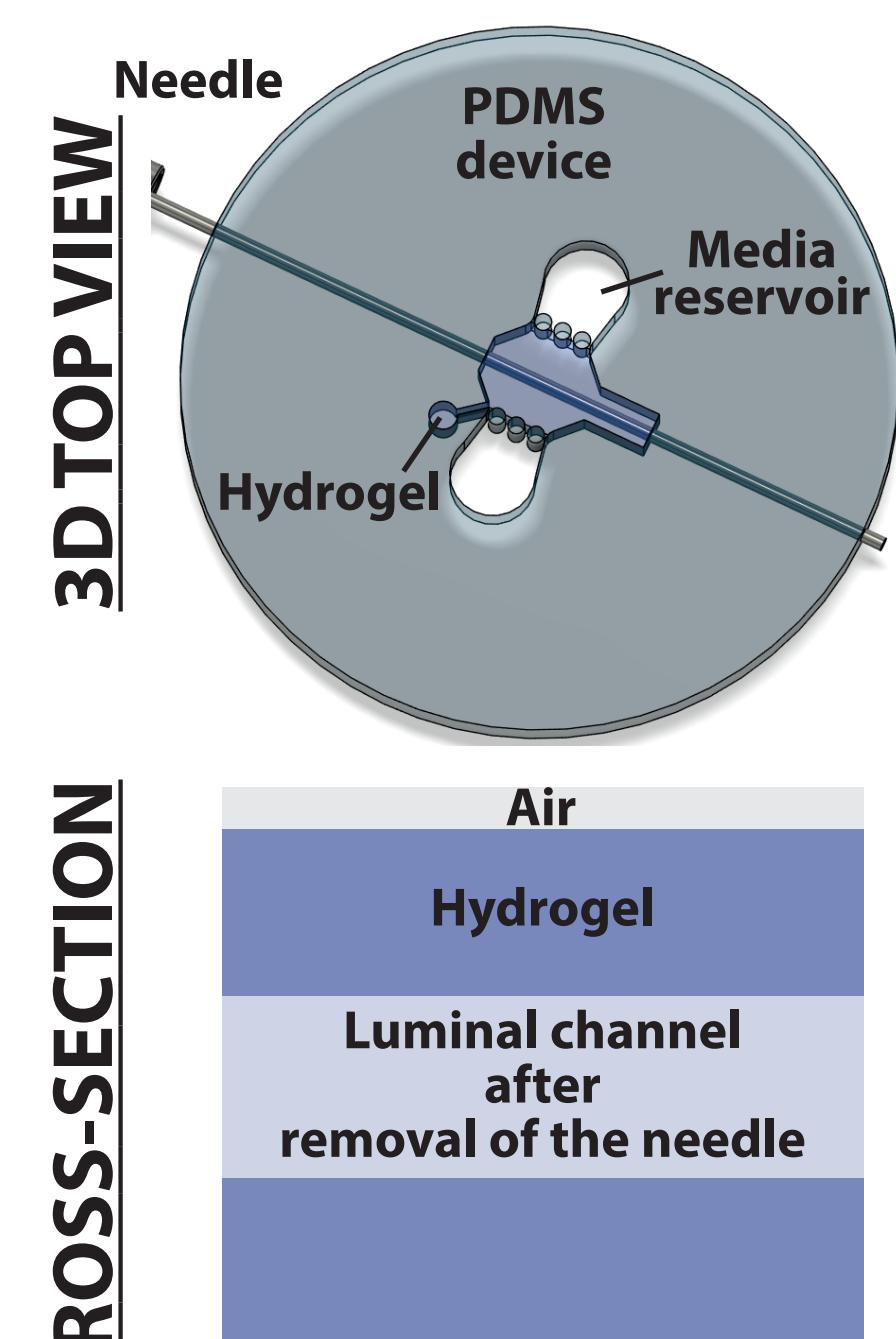


Using a 3D printed mold and a 250-600 μ m needle, we generated a PDMS device with a lateral channel crossing a central chamber flanked by two reservoirs for nutritive media.

Using the same principle with hydrogel, we shaped a lumen by polymerizing hydrogel around the needle.

Actual 3D-printed mold

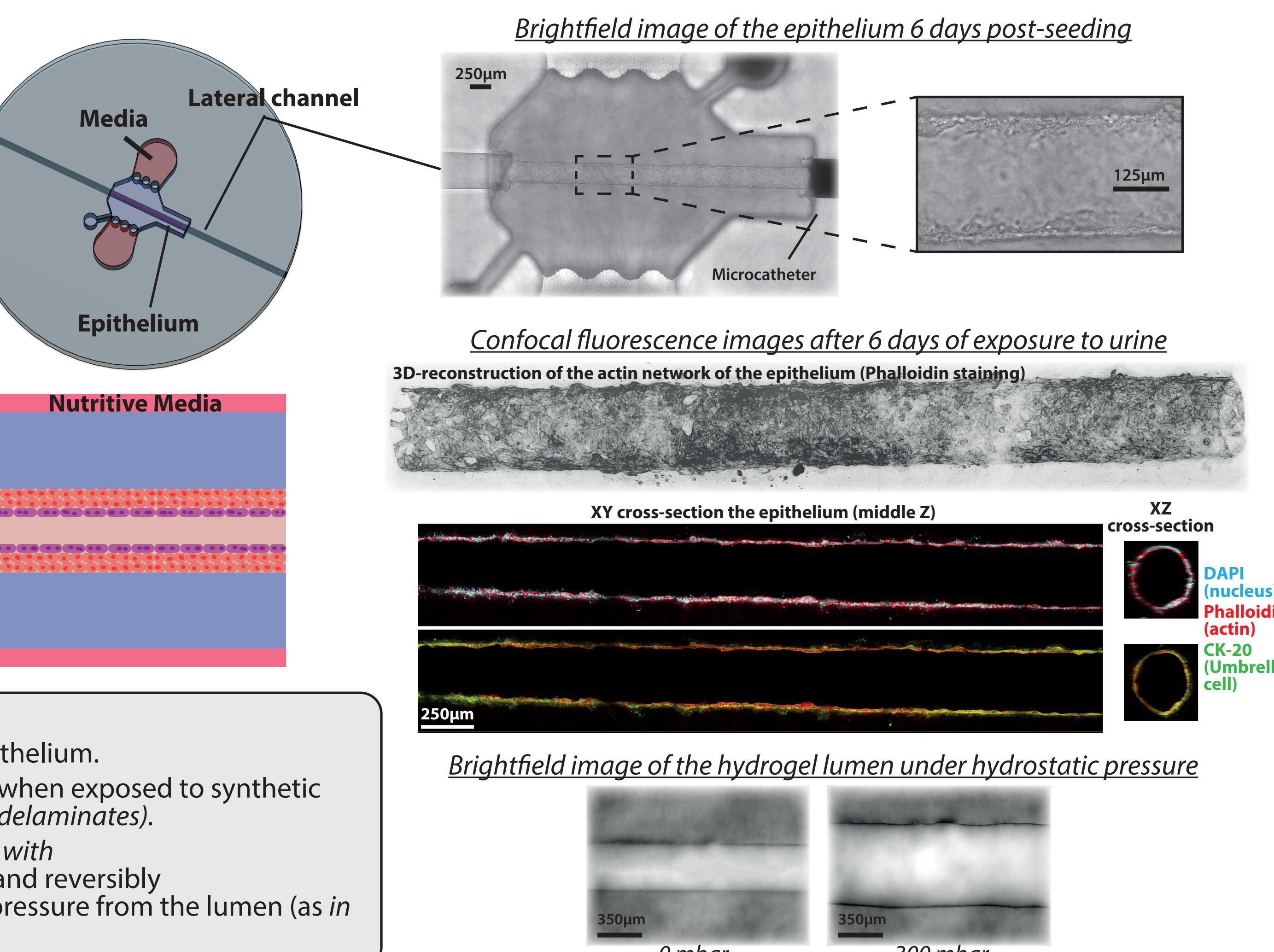
Actual microfluidic device



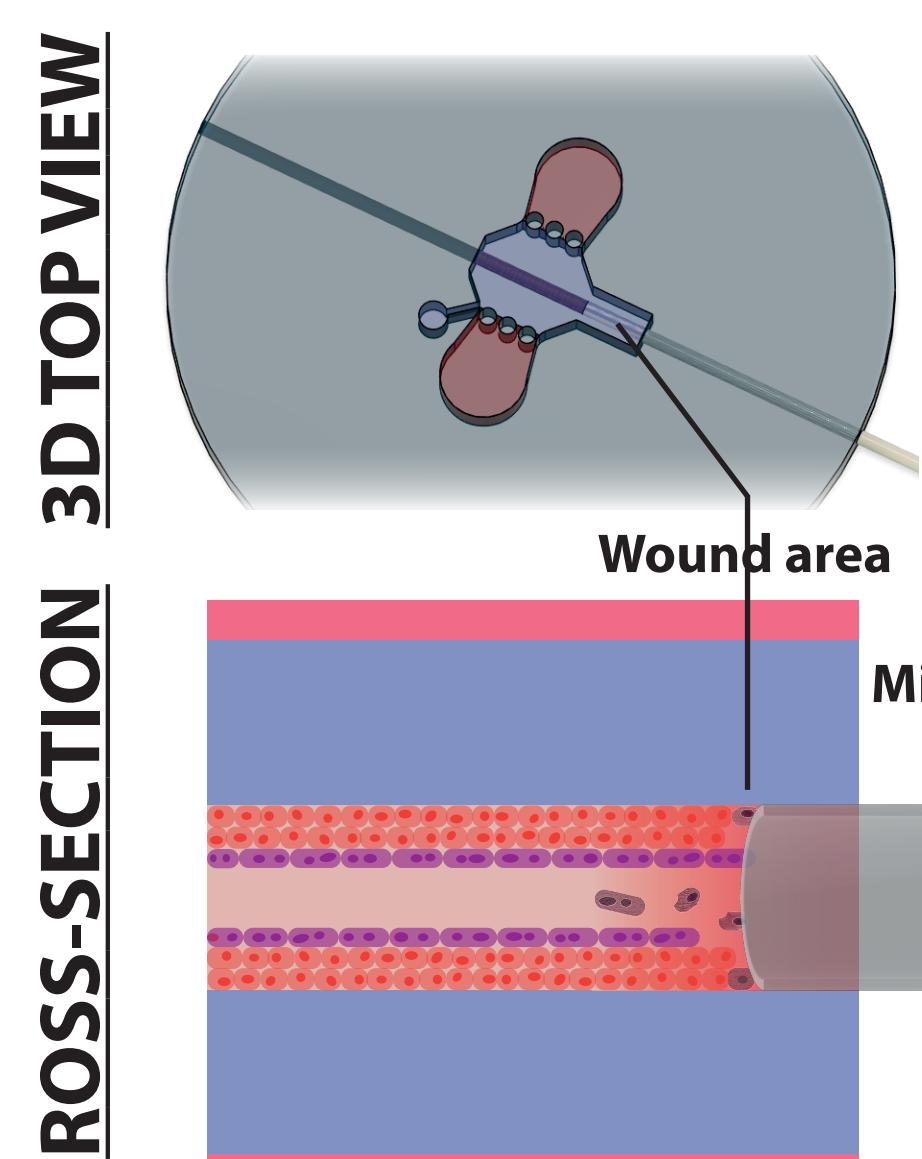
- 1) Seeding bladder epithelial cells from the lateral channel (H6215)
- 2) Perfusion of epithelial media for 6 days
- 3) Perfusion of synthetic urine

CURRENT PROGRESS:

- Cells form a stratified epithelium.
- Apical cells differentiate when exposed to synthetic urine (but the epithelium delaminates).
- The lumen (without cells, with cells is WIP) is accessible and reversibly stretchable using static pressure from the lumen (as *in vivo*), for hours of cycles.



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 perform 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.

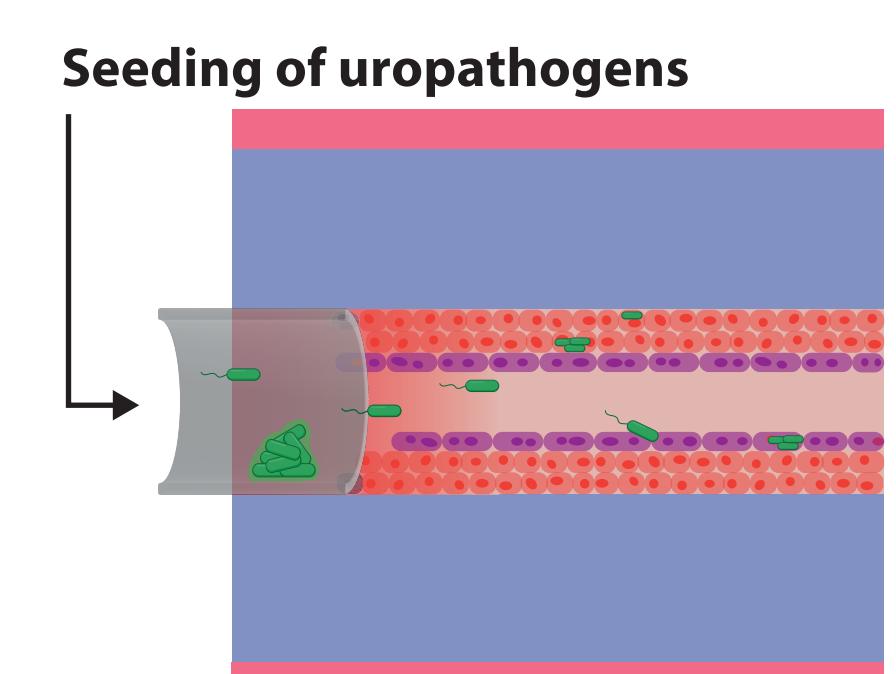
Characterization of the infection

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 Communities³?



QUESTIONS

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

How do flow, tissue stretching, and urination dynamics affect urothelium properties and pathogen virulence?

Can we use this model to study polymicrobial infections or to test treatments and catheter materials?

REFERENCES

¹Adapted 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).

²Paduthol, Gauri et al., Human bladder microtissue model to study chronic and recurrent UTIs, unpublished.

³Sharma, K. et al. Dynamic persistence of UPEC intracellular bacterial communities in a human bladder-chip model of urinary tract infection. *eLife* 10, e66481 (2021).



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