SMGroup

Empathic Design Of Materials For Urinary Tract Infections

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Published Date: April 10, 2016

INTRODUCTION AND PURPOSE

Urinary tract materials needed for urinary devices were developed and used for managing the unfortunate and inconvenient medical conditions involved in the malfunction of urinary systems through both infectious agents and through other disorders of the urinary tract. While the most important purpose of urinary tract materials is to provide for a dependable structure for the function of urinary devices such as to drain urine and abscesses appropriately, they are ultimately designed to improve the quality of life of patients with urological problems by providing comfort in the management of such medical conditions. Thus, urinary tract materials need to satisfy a wide variety of constraints to provide for this elevation in the quality of life of patients and the design of such materials would greatly benefit from an empathic design approach that considers design modifications from the users point of view. (Note: this is not the same as empathetic design [1]).

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The purpose of this book chapter is to provide a summary of materials composition-property-performance perspective and current understanding of underlying mechanisms in a question-answer format based on recent research in the field of urinary tract infections (UTI) targeted at post graduates and research scholars in the field urging them to consider the use of an empathic design approach, thus furthering development towards "a set of ideal urinary tract material designs". Figure 1 lists the different areas and empathic design classes informing material choices for use in urinary tract devices. A patient's quality of life contextually depends on the patient type that is afflicted by the urological condition. The patient's urological condition ultimately decides the function of the device that is to be used which then determines the form to be used and which in turn informs the material characteristics. In addition to the form dictated by functional requirements, certain factors that are involved in applicability of the device need to be considered. From the empathic design approach, factors including infection, device function loss due to contamination or blockage and discomfort during insertion and use feature prominently. All of the classes of factors provided here need to be addressed in improving the design of urinary tract materials. Only the most important factors belonging to the listed classes are highlighted in this write up and this list is by no means exhaustive. The reader is encouraged to follow the empathic design approach by placing the experience and quality of life of the patient at the center of their design initiative.

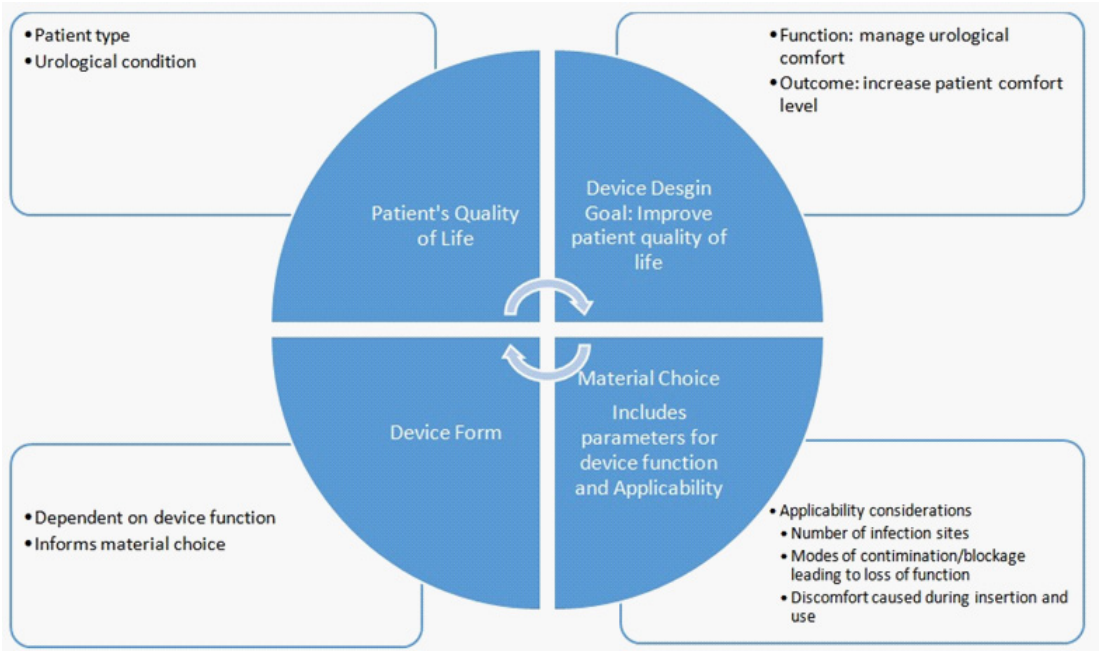

Figure 1: Flow diagram of the systems, interactions and the classes of empathic design approach involved in the creation of a urinary tract material.

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To understand the information listed in this chapter, it is useful to start with a basic definition of the urinary tract. The European association of urology defines the urinary tract (Figure 2) as "The organ system which produces and transports urine through and out of the body. It includes two kidneys, two ureters, the bladder and the urethra. The urinary tract is similar in men and women, only men have a longer urethra." Infection in any one of these components of the urinary tract leads to a type of urinary tract infection, which may or may not be in conjunction with the introduction of artificial/synthetic materials or procedures.

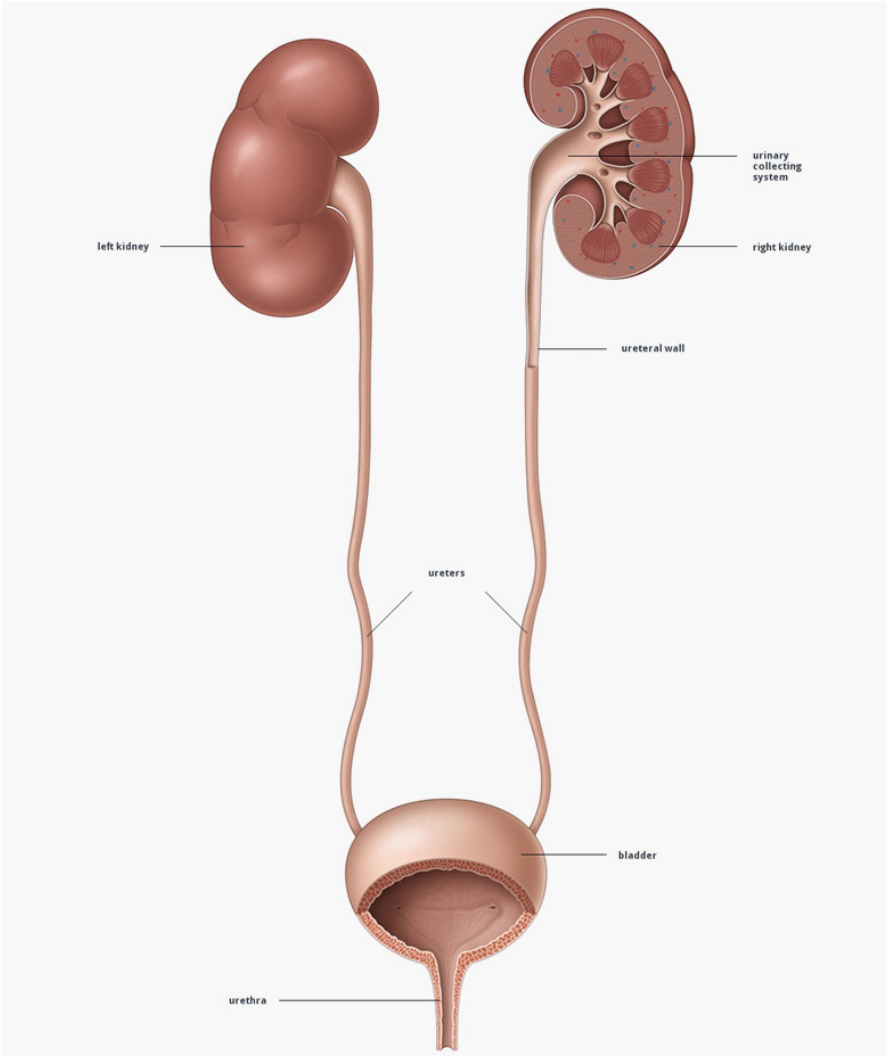

Figure 2: Illustration of all the important segments comprising the urinary tract.

Source: http://patients.uroweb.org/kidney-ureteral-stones/symptoms/

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WHAT DOES IT TAKE TO DEVELOP A UTI?

From a point of view of developing a urinary tract infection, there are 3 systems involved:

- The urinary tract is composed of various fluids, tissues and cells lining it: In the earlier parts of this book you learned about the various aspects of the urinary tract, the fluids it channels, about the cells and tissues that line the same. For the purposes of this discussion, in summary, the urinary tract consists of the kidneys, which filters the blood producing urine, the ureters, which carry urine from the kidneys to the bladder, the urinary bladder, which stores urine, and the urethra, through which urine from the bladder exits the body. Urine in a healthy individual has a neutral to slightly acidic pH and consists primarily of soluble waste including salts and toxins, generated during cellular metabolism. It is currently accepted that microorganisms do not normally reside in the urinary tract. More recent evidence suggests that urine is typically not sterile, however, the microbial load in a healthy individual should be very low [1,2]. When microbial load becomes higher, clinically defined as bacteriuria with a $\geq 10^4$ CFU/ml in void midstream urine or $\geq 10^2$ CFU/ml in catheterized urine sample in men, they are at risk of developing a urinary tract infection (UTI). In women, bacterial counts are less reliable and UTIs may occur at a lower microbial load, and thus detection of pyuria (ie., ≥ 10 leukocytes / microliter) is a valuable diagnostic tool for women.

- The most common type of infection of the urinary tract is a bladder infection (cystitis). Bladder UTIs may ascend from the bladder into the kidneys leading to a kidney infection (pyelonephritis) [2,3]. Both of these types of UTIs are more common in females than males. An infection of the urethra alone (urethritis) is most commonly caused by a sexually transmitted microbial pathogen (i.e Chlamydia, Gonorrhea). Bladder UTI's may be asymptomatic. Consequently, screening and treatment for UTIs are recommended in certain groups such as pregnant women. While kidney infections usually do not cause permanent damage, if left untreated, it has the potential of leading to serious complications and may become life threatening. There are various causes and contributing factors to development of UTI's ranging from poor general health or hygiene, to obstructions (i.e. kidney stones, structural abnormality) to acquisition of antimicrobial resistant pathogens. It is currently accepted that microorganisms that lead to UTI's gain access to the urinary tract through the urethra. Most acute uncomplicated UTIs is believed to be caused by uropathogenic microorganisms from the intestines, especially *Escherichia coli* [3,4] (75-95%). Motile uropathogenic microorganisms, such as *Proteus mirabilis*, are better able to ascend to the kidneys.

- Modes of introduction of microorganisms to the urinary tract: The two primary ways in which microorganisms can be introduced in catheter associated UTIs is extraluminally during the process of insertion in to the urethra or intraluminally by swimming up from the collection bag [4,5]. It is currently accepted that approximately 20 percent of hospital acquired blood infection (bacteremia) results from UTI's with an associated mortality of 10 percent [5,6]. In the case of

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catheterized individuals (indwelling or intermittent), symptomatic UTI are typically confirmed with detection of ≥10^3 CFU/ml of uropathogenic bacteria in the urine [6,7]. Although a threshold of ≥ 10^2 CFU / ml of urine is diagnostic of bacteriuria, as stated above, most clinical labs cannot quantify microbial load below 10^3 CFU / ml urine using standard culture methods. 10-25% of catheterized patients with bacteriuria develop UTI's [7,8]. Asymptomatic UTIs are traditionally diagnosed in catheterized individuals found to have ≥10^5 CFU/ml of uropathogenic bacteria in their urine [6,7].

HOW DOES CATHETERIZATION AFFECT URINARY TRACT INFECTION ETIOLOGY?

The current set of catheter associated UTIs can be broken down to mainly bacterial and fungal forms of infections. The etiological spectrum is different than that found in individuals that develop UTI's not associated with catheters, for example, Candida fungal infections almost never cause UTIs in the absence of an indwelling catheter but make up approximately 13 percent of catheter associated UTIs [8,9].

Catheterized patients with co-morbidities such as diabetes or undergoing antibiotic or immunosuppressive therapy are especially at risk of developing candidiasis, and less commonly *Aspergillus* and *Crypotoccus species*, UTIs. It has been reported that among cases of candiduria, *candida albicans* is the most common followed by *Candida glabratta* (together accounting for 25% to 35%) with *Candida tropicalis, Canidida krusei, Candida parapsilosis* and mixed species making up the rest of the isolates in fungal UTIs studied so far [9,10]. Historical accounts outlining all the progressions in urinary tract infections are available in the literature [2,3,10,11].

Catheter-associated UTIs are the most common type of nosocomial infections accounting for 40% of all hospital acquired infections [11,12]. The risk of colonization by various uropathogenic microbial species and the risk of developing UTIs appear to depend to some degree on the length of time an individual is catheterized. In short term catheterized individuals, less than 24 hours to about 7 days, the risk of infection is 10 to 30% (3 to 10% per day). Some report an incidence of developing UTIs as high as 50% in short-term catheterized patients [12,13]. *Escherichia coli* is the most common infecting species, however it accounts only for about 25-27% of isolates as opposed to 75-95% of cases of UTIs not associated with catheters [13,14]. Other associated species include *Klebsiella pneumoniae, Enteroccocus sp., Pseudomonas aeruginosa, Staphylococcus epidermis, Staphylococcus aureus* and *Enterobacter sp*. [15-19]. The general risk factors include, duration of catheterization, microbial colonization of the drainage bag, absence of antibiotic use and errors in catheter care.

In the US, approximately 100,000 patients have urinary catheters in nursing homes and many are catheterized for several months [19,20]. Most of these patients are bacteriuric by the end of 30 days [11,12]. In long term (greater than 28 days) catheterized individuals, 95% of urine samples are reported to be positive with polymicrobial species with more common species among them

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being *Escherichia coli, Enterococcus sp., Candida sp., Pseudomonas aeruginosa, Proteus mirabilis, Providencia stuartii and Morganella morganii* [3,4,8,9].

The key factors proposed to be the reason for this increased risk of UTIs and the observed etiological shift is 1) the ability of microorganisms to form biofilms on devices such as catheters, which are both difficult to effectively treat externally and difficult to eradicate by host defenses, 2) the reduced exposure of microbial biofilm on the device to host defenses, thus facilitating microbial colonization and biofilm growth of native and environmental contaminants, and 3) the fact that patients requiring catheterization often have existing co-morbidities that compromise their immune response. The generally accepted definition of microbial biofilms are a population of microorganisms enclosed in a matrix of self-secreted polymers (e.g, polysaccharides, DNA, proteins, etc.) attached to each other and irreversibly attached to a surface [20,21] (Figure 3).

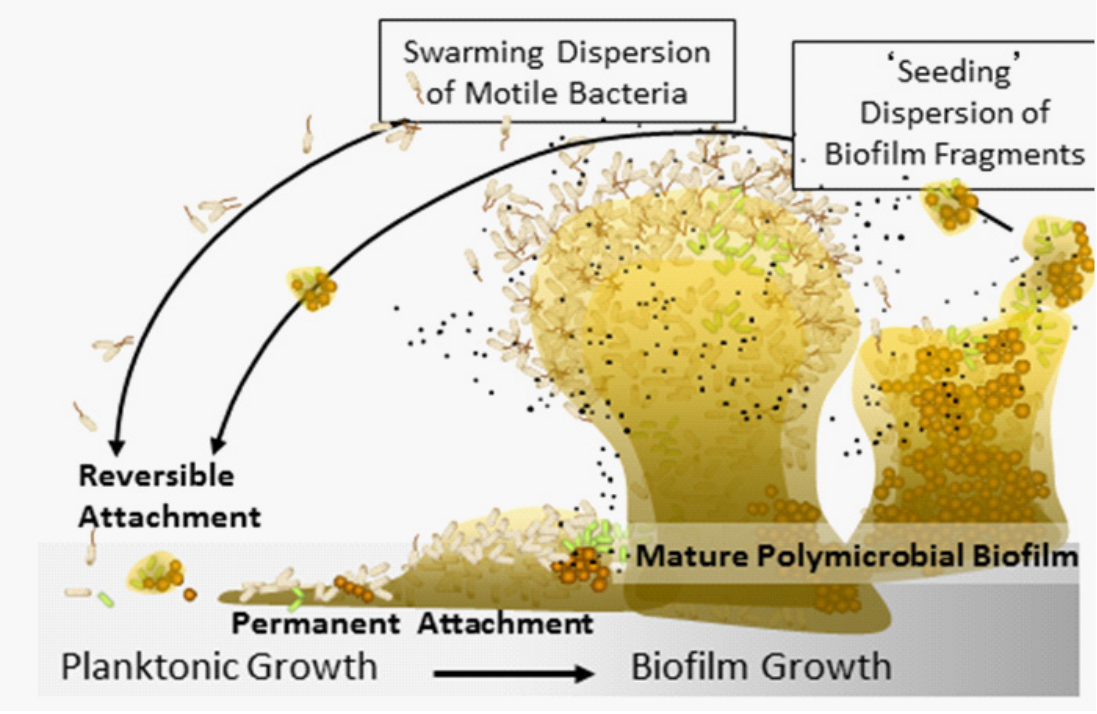

Figure 2: Illustration of a hypothetical biofilm formation following the steps reversible attachment, EPS production and irreversible attachment and replication, micro-colony formation, differentiation in to biofilm phenotype, release of planktonic cells for colonization of other areas.

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PROCESSES LEADING TO THE INFECTIONS ASSOCIATED WITH URINARY TRACT MATERIALS

Within minutes of placement of the biomaterial in the appropriate environment with the necessary fluids, a conditioning film is deposited on the surface of the implanted material comprised of dissolved proteins, salts and other organic components [22,38]. Microbial biofilms that form the basis of chronic urinary tract infections result from the same fundamental, secondary bonding forces (beyond the primary valence bonding regimes) arising out of the electronic states of the assemblages of chemical elements [23,39]. The most universal of these being the Lifshitz-van der Waals (LW) forces which depending on the interacting surfaces and intervening media can be attractive or repulsive [24,40]. Based on the like charges on the interacting surfaces, repulsive electrical double layer interactions (EL) arise. Additionally, the electron donor-acceptor nature of the interacting surfaces result in Lewis acid-base (AB) interactions, subsets of which include Bronsted acid-base and specific interactions. Specific to high electronegativity elements, namely fluorine, oxygen and nitrogen, display hydrogen bonding interactions defined as "an attractive interaction between a hydrogen atom from a molecule or molecular fragment X-H in which X is more electronegative than H, and atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation" [25,41]. Hydrogen bonding is a major contributor to the so called "hydration forces" and "hydrophobic effect". Hydrophobic materials tend to strongly attract each other in aqueous media and this is termed the "hydrophobic effect" [26,42]. Finally, by virtue of the thermal state of the system, the surface interactions are characterized by Brownian energy.

Following the formation of the conditioning film, if the fluid environment has microorganisms, the next step in the process is the formation of a biofilm. As stated previously, the generally accepted definition of microbial biofilms is a population of microorganisms enclosed in a matrix of self-secreted polymers (e.g, polysaccharides, DNA, proteins, etc.) attached to each other and irreversibly to a surface. Although this is widely accepted, another definition of biofilms namely "functional biofilms" has been advanced on the basis of its inherent ability to tolerate high concentrations of antibiotics and antiseptics, even in the absence of natural (genetically encoded) resistance [21,27]. In light of analysis of biomaterial colonization and infections, the latter definition might be more appropriate. This definition defines the point at which biofilm become fully mature and are most difficult to remove. When incorporated in biofilm study design, this definition sets a standardized reference point, and thus improves the ability to conduct comparative analysis of outcomes from different studies. Figure 3 is an illustration of the above described process of biofilm formation, the favored form of growth for most microbial species. It is important to understand that microbial biofilm can form on both biomaterials and biological tissues. Furthermore, biofilms formed on indwelling devices can act as a microbial reservoir leading to the observed increase in the risk of developing UTIs in catheterized individuals.

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As described in the earlier sections infections can be a single dominant species or can be mixed populations of opportunistic pathogens. *Proteus mirabilus*, a facultative anaerobic gram negative bacterium of Proteus species accounts for up to 90% of Proteus species community acquired infections in humans. [28,43] Proteus species generates the enzyme urease and has the tendency to swarm, facilitating its ability to cause UTIs [23,44]. P. mirabilus is reported to have the greatest ability among Gram-negative organisms to attach to biomaterials most commonly used in urinary catheters (Jacobsen SM, Stickler DJ, Mobley HL, Shirtliff ME. Clin Microbiol Rev. 2008 Jan;21(1):26-59. doi: 10.1128/CMR.00019-07).

HOW ACTIVE IS THIS FIELD?

A general search for UTIs on Web of Science pulls up approximately 123000 articles, reviews and other forms of publications. However, the field starts recognizing the importance of biofilms in association with UTIs only from the 1990s onwards with a total of 998 articles and over 2500 citations per year over the last 3 years. This shows that the field is gaining a lot of traction and indicates the field is ripe with many opportunities to solve key problems especially in association to the mitigation (and perhaps alleviation) of microbial biofilms on foreign objects such as catheters. The above search with an added "materials" filter yields about 138 publications with 125 original articles, meeting and case reports (Figure 4).

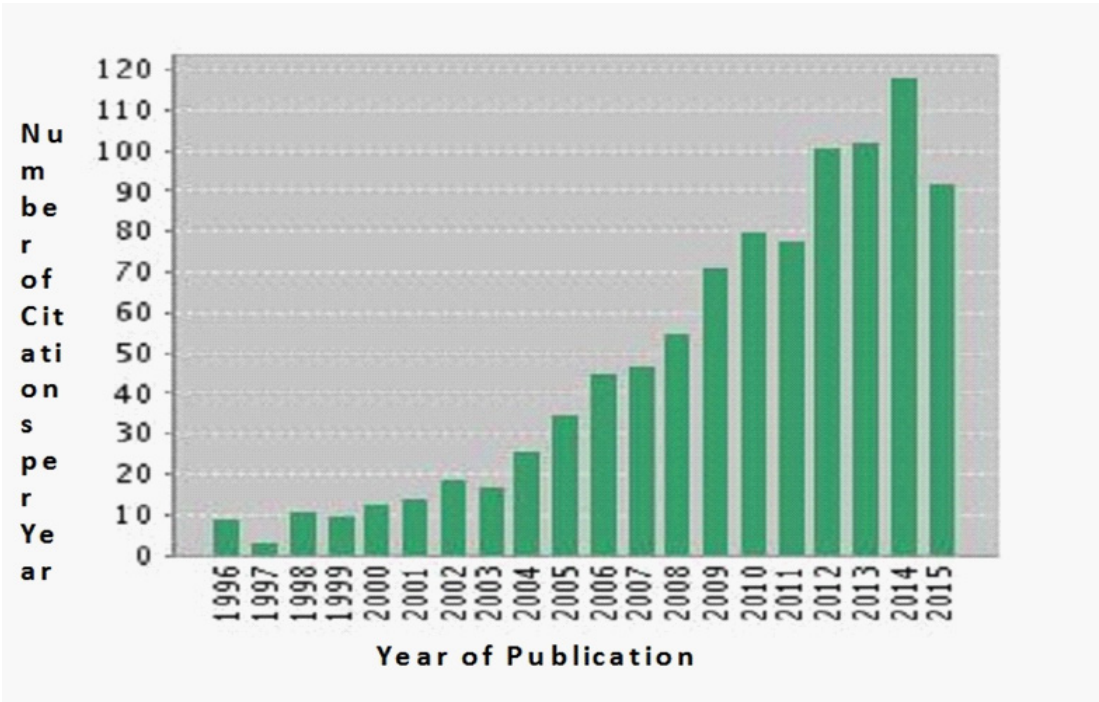

Figure 4: Citation activity associated with publications in the field of urinary tract infections overlapping fields of study in biofilms and materials research.

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MATERIALS & METHODS

Material Systems

What are the types of materials systems that may lead to bacteremia and bacteriuria?

The key material systems are generally divided in terms of facilitating patient function [22,31]. More specifically, the main processes requiring material intervention/assistance can be divided in to urinary drainage, blood supply aids and stool collection. For urinary drainage, the most common material systems used are catheters, stents and incontinence pads. The most commonly used blood supply aids are usually categorized as intravenous lines, dialysis lines, grafts, intravenous catheters, valves sutures and needles. Stool collection is normally performed using diapers and pads. The overall value of such systems is approximately $86 billion a year globally and increasing at 7% per year.

With regard to the introduction of foreign material surfaces in to the body, the following biomaterial systems dominate in terms of frequency of application [23,30]:

- Urethral and suprapubic catheters
- Urethral and uretral stents
- Nephrostomy tube

Urinary catheters are used for the purpose of preventing urine retention, controlling urinary incontinence, collecting urine during surgery and to measure urine output. They are inserted into the bladder through the urethra. The numbers of patients in which urinary catheters are inserted exceed 5 million every year.

The Foley catheter, the most common type of urinary tract catheter, has an inflatable balloon to hold its place in the bladder. It was invented in 1936 by Frederick B. Foley [24,32]. Despite the life-saving nature of this device and other catheters which perform similar functions, they suffer from an array of complications (Figure 5).

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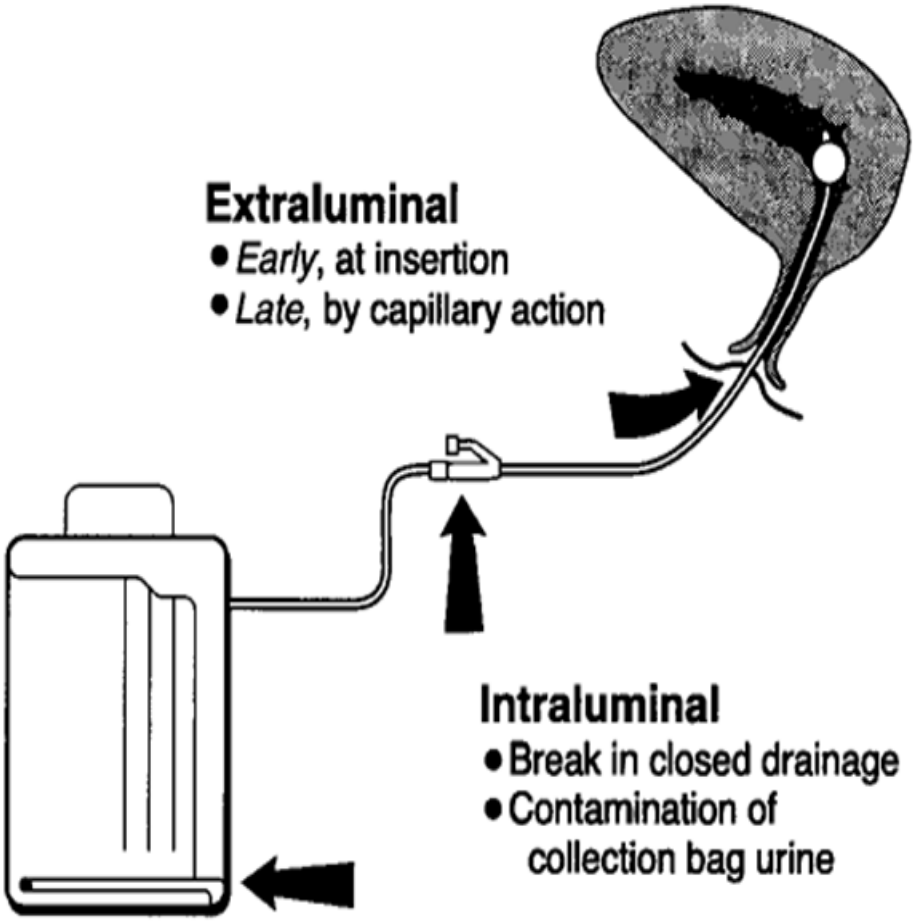

Figure 5: Potential problems in a Foley catheter.

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Which material classes are being utilized?

Through the ages many different types of materials have been used as urinary biomaterials. These include metals such as gold, silver, tin and lead, papyrus used by the Egyptians and sea animal skins stuck together by glue derived from cheese [25,33]. Other materials of the 17th century included cloth catheters impregnated with wax or lead for improved pliability and woven silk catheters and woven silk over probes [24,36]. Natural rubber catheters were introduced in the 19th century but had mechanical property issues due to softening at body temperatures and stiffening at colder temperatures which were addressed by Goodyear's vulcanized, durable rubber catheters and Nélaton's flexible red rubber straight catheter [27,28,35,36].

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What other materials have been used categorically?

Examining the materials systems used in urinary tract available to date, one can summarize the ideal characteristics for each application and the most common material currently used. For example, silicone is currently the preferred material, recommended by the International Continence Society, for Foley catheters used in long-term applications (6-8 weeks). Table 1 summarizes the characteristics that would make up an ideal urinary tract material.

Table 1: Ideal Characteristics of Urinary Tract Materials.

Group	Characteristic
Compatibility	Inertness to biological environment/ non-allergenic Resistant to Infection and biofilm buildup Encrustation build both under infected and sterile cases Cause no discomfort
Stability	Chemical resistant under urine conditions Remain in place after deployment Flow reassurance: long-term proper flow rates
Cost	Affordable with all functionalities in place

Materials and Performance Criteria

As described in the previous section (Table 1), polymers and metals are predominantly used as the classes of materials used in making biomaterials for the urinary tract. The synthetic polymer materials especially for the use of catheters include silicones, silicone copolymers of various kinds, specifically styrenic/ethylene/butadiene elastomers, aliphatic thermoplastics/ thermoplastic elastomers and polyurethanes. Several metals including stainless steel nickel-titanium alloys and titanium superalloys are used in making stents for the ureter and the urethra. Additionally, resorbable materials are used for the construction of stent materials for the urinary tract, these include poly-L-lactic-coglycolic acid.

Coatings of various kinds have been used to achieve many interfacial performance characteristics. These coatings have been applied to urethral and ureteral stents and to catheters for the purposes of reducing encrustation, biofilm formation and reducing discomfort during insertion by lowering the coefficient of frictions. Several hydrophilic polymeric materials aiding the structuring of water at the material-tissue interface have been used for this purpose including polyvinylpyrrolidone, polyacrylamide, polyethylene glycol and polyvinyl alcohol [29,30,37,38]. While this reduced coefficient of friction during insertion, it had significant effects in terms encrustation which required other coatings such as drug eluting or controlled release coatings [31,39]. Examples of these are biofilm inhibiting antibacterial agent facilitated release coatings, such as silver, ciproflaxin, rifampin, minocycline and nitrofurazone or molecules that act by reducing binding such as heparin based coatings [29,32,33,37,40,41] or encrustation prevention by phosphorylcoline groups of compounds and pentosan polysulfate sodium [29,37].

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Methods for Studying Infections Associated with Urinary Tract Materials

What are the methods and models for studying the fouling/infection and encrustration processes? There are several procedures developed by the American Society for Testing and Materials (ASTM) to filter biomaterials appropriate for *in vivo* testing. Several models of the encrustation process exist including Cox model, Gleeson model, Holmes model and the artificial urine model, where the researchers showed that it was possible to reproducibly produce encrustation in tubes *in vitro* and that analysis proved that this is comparable to encrustation *in vivo* [34,42].

What are the Best Methods of Quantification of Biofilm Formation?

There are few high throughput models to study catheter performance and a few of these involve the use of *in-vitro* environments and synthetic urine [43 35, 44 36]. One published model offers a promising high throughput method to test a variety of materials using an *in-vivo* mouse model system that is not limited to only female mice, as more commonly used in other studies, which appears to more closely mimic human urinary tract conditions [45,37].

RESULTS

Catheter Types and Favorable Performance Characteristics

Catheter materials are made of several types, the most common of which are latex and silicone. In order to combat infections and also improve compatibility, several approaches have been put forward since the invention of the latex catheter. Among the material types used, polymers outweigh most other materials as the preferred material type [45,46]. Among polymers PTFE®, silicone, latex predominate as the structural materials. Among these, PTFE® coated catheters have been shown to have high levels of toxicities [46,47]. Whereas, silicone with its favorable biocompatibility also displays excellent UV and chemical resistance. Among commercially available catheters including, hydrogel/silver coated latex and silicone coated latex, silicone catheters resulted in some of the longest periods before blockage [45,46].

Another approach to the control of urinary tract infections due in the use of catheters is by incorporating antimicrobials and disinfectants in natural rubber resins.

Continuous draining of catheters with the addition of antibacterial agent or disinfectant to the collection bag is an option [47,48], whereas, controlled release of antimicrobials from glass or polymeric materials is another alternative approach [48-50]. Another *in-vitro* study used triclosan dip coated silicone catheters which did not result in encrustation with *Proteus mirabilus* as the test species versus all control catheters resulting in blockage [50,51]. Several properties including biocompatibility, toxicity and structural/mechanical stability of the materials used for the construction of catheters may be affected by the incorporation of antimicrobials [51,52,53].

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Silver, silver oxide, PTFE® and silicone coatings were proposed as alternative coatings for preventing biofilm formation. Silver based coatings however have been reported to have mixed results. One study reported the increase in the amount of Staphylococcal infection [45,46], while another study question the potential benefits silver coated catheters [53,54]. Statistically significant differences were observed in a study based on silver coated catheters [46,47,51,52].

PTFE® coated catheters while showing high lubricity and low surface energy have been reported to be among the most toxic catheter materials and need further research identifying ways to make them more biocompatible [46,47]. From the perspective of biocompatibility and increasing lubricity for ease of insertion hydrogel coatings have been employed for catheters [54-57]. While hydrogel based catheters offer many advantages they often have poor structural/mechanical performance [45,46] and normally show the tendency for rapid encrustation [48,49,52,53].

Silicone (or polydimethyl siloxane) have been used for constructing most of the parts of the Foley catheter [55,56]. A literature search reveals some inconsistencies through mixed reports in the prevention of biofilm formation on silicone catheters. Silicone materials have been reported to have maximum fouling prevention [56,57], while other studies indicate maximum bacterial adhesion [52,53,57-59].

Encrustation and blockage based complications have been shown to occur as result of biofilm formation in most, if not all, of the materials and coatings combinations used to date for making catheters. A review article emphasizes the need for further research in to the development of coatings or better materials for catheters. The authors stated that "although it has been 70 years since the Foley catheters were first introduced, the problems of infection and encrustation still remain" and "little attention has been paid to the contributory effects of materials and design of urinary catheter" [45,46].

DISCUSSION

One unique hypothesis that has been proposed is that, the injury to cells due to the insertion of materials in to the urinary tract could be a primary cause for and accelerant of the encrustation due to the up regulation of proteins involved in wound healing response. While this needs to be explored further, the factors contributing to encrustation are numerous and include interfacial forces and microbial populations, duration of exposure to urine and individual biochemistry [59,60].

It is possible that cellular injury in response to the presence of urinary tract biomaterials may be an important determinant in the promotion and progression of encrustation because many of these up-regulated proteins are also known for their role in wound healing.

Cellular injury is certainly one of the design factors that are of less relative importance when it comes to the critical functions of the catheter. Empathic designs, which do take in to account this

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design factor are few and far between. Some examples such as hydrogel lined catheters [44,61,62] have taken this in to account in order to improve patient quality of life, however on the flip side do not perform as well mechanically. Furthermore, a definitive model of material surfaces needed to prevent cellular injury is yet to be developed.

There are several exciting areas of research for using active methods to reduce the incidence of infections associated with urinary tract materials [60,63]. One such area involves the approach known as iontophoresis, where diffuse ion flow occurs through the application of a low intensity electric field and this could be achieved with low intensity direct current [61,64]. *Proteus mirabilus* in urinary flow models for silicone catheters with silver wire inserts in the lumen showed delays in blockage by nearly 120 hours from the 20 hours in the control case. Quorum sensing, cross species chemical signalling, takes place through release of small molecules that serve to communicate across biofilms. Inhibiting these is another novel approach to preventing biofilm growth and subsequent infections. Some initial investigation in both *in-vitro* and sheep models have been conducted but further research is needed to translate [62,65] these initially promising results from the laboratory to the clinic.

Vibroacoustic technology is another unique approach to solving the biofilm formation and encrustation problem and early studies with a rabbit model show an extension in maintaining sterile urine from 48 hours in the control case to 216 hours in the surface acoustic wave coating [63,66].

While many of these breakthroughs are exciting research projects, they only demonstrate proof of concept in some prototypical form. This area of research could benefit from a major empathic design overhaul in their translation from R&D lab to clinic. Given the wide array of health-care facilities which use catheterization frequently and on large number of patients, it would be very useful to develop a collaborative lab-to-clinic translational program where patients who need catheters are given an option to participate in lab prototype devices with appropriate medical and ethical considerations involving patients, R&D labs, catheter companies and health-care facilities. This would then provide the development path to iterate on a deployable design, with learnings from each entity applied in a patient centric manner, in what is akin to concept and use testing even before the creation of an improved physical prototype. Such a program could in theory provide rapid feedback for R&D labs and industry partners in iterating through empathic catheter designs from the patient centric perspective with adequate input from medical practitioners and industry leaders. Thus key design elements that are vital to the functioning of the urinary device with improvements to the patient's quality of life will be successfully identified. A major consequence of this empathic design approach is that the value proposition is clearly established and time and monetary investments in clearing regulatory hurdles will become less risky and worthwhile.

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FRONTIERS AND OUTLOOK

Emerging Technologies

There are several innovations in the field of materials surfaces/interfaces. Theoretical analysis of experimental data of biofilm formation on patterned surface shows that trapping of air in a robust way decreases the probability of attachment and hence reduces biofilm formation [64,67]. While this approach did not consider all of the empathic design classes, two important factors were taken in to account. Firstly, consideration was given to infection by interfering with (reducing) biofilm formation and, secondly, to reducing the use of antibiotics that might lead to grave consequences due to emerging antibiotic resistant strains, especially under conditions of long-term use.

Other studies have shown that reduction in biofilm formation on patterned topography is valid for more than one type of microorganism [65-71]. It is important to consider the nature of slip and flow past rough surfaces, notably those with a durable superhydrophobic Cassie-Baxter state [71,72,74,75], as a potential means for fouling and infection control. Additionally, there is an another approach that uses the presence of thermodynamically stable liquid films that utilize flow of liquids in textures or through porous media generally referred to as liquid impregnated surfaces [72-76]. These advances need to be taken in to account and with appropriate theoretical and experimental screens to design next generation interfaces in the materials used in the urinary tract to take advantage of interfacial engineering.

However, most of these observations were conducted with less than 48 hours of exposure time to biofilm growth solutions and experimental studies to quantitatively confirm the effect of patterned topography on biofilm formation surfaces resulted in no statistically significant differences [75,78]. Hence further studies of these phenomena are needed to determine underlying mechanisms is crucial to obtain functional materials for the urinary tract.

While mimicking tissue and its properties are necessary to produce manufacturable synthetic/alternative material types, autologous tissue engineering to produce desirable implant materials is an exciting area of research with some key early prototypes already demonstrated [76,79]. These could provide the ideal combination of characteristics expected of materials designed for the urinary tract.

Where Does the Field Seem to be Headed?

Biomaterials for the urinary tract have very real challenges from several material property-performance perspectives. The intersection of bacterial biofilm based infectious disease research and materials science is a rapidly growing field with many emerging insights which are leading to key developments in the engineering of surfaces. At the same time studying complex biological systems effectively has its own challenges multiplied by the varying nature of patient biochemistry and microbiomes. Interdisciplinary collaborative efforts in well-defined surfaces/interfaces and bulk mechanical properties combined with reproducibly quantifiable microbial studies is key to modeling the appropriate biomaterials systems to achieve optimal output.

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Another interesting approach uses physical dislodging by creating a differential strain by modifying the wall of the catheter to contain a chamber in addition to the main drainage channel. This approach allows for an on demanding cleaning of the occluded to catheters. However it needs to be pointed out that the debonding is not a 100% and the infection itself has not been prevented using this approach [77,80].

In almost all of the above approaches, taken individually, the improvements are usually within an order of magnitude in comparison with the control in terms of time frames. While these approaches hold promise for the short term catheterization periods and the search continues for strategies needed to obtain solutions to the problems encountered by long term catheterized patients. It behooves researchers and industry leaders alike to build bridges and complete the feedback loop with patients in carrying out future designs. Such empathic design approaches are essential to accelerate the pace of innovation in materials designed to manage urinary tract infections.

Questions to Ponder

Do materials systems have to be entirely inert? Since it is harder to produce materials that are capable of being completely inert, it may be better to produce favorable reactions improving the adoption of biomaterials in to urinary environment. For instance, controlled dissolution of the inner wall lining atomic layer or nanometer layers at a time could yield the necessary response to counteract several of the dynamic challenges in the urinary tract environment.

Why remain passive? Active/responsive designs are ushering the next generation in urinary tract materials design with the purpose of retaining structural and implant functionalities while bringing a whole host of novel, favorable surface active and interfacial properties.

Understanding and integrating all the empathic design classes including frontier research insights into biofilm processes, active material systems and tissue engineering will bring us closer toward reaching the goal of developing ideal materials systems to prevent device associated urinary tract infections.

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