Bacterial Interference in the Urinary Tract

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None of this substantially helps the patient who requires long-term urinary catheter drainage.

In Houston in 1999, Hull et al. [1] and Trautner et al. [2] identified an Escherichia coli isolate in a culture of urine obtained from an asymptomatic patient; the isolate reproduced readily in urine, and subsequent studies have shown that its presence prevents other urinary pathogens from adhering to a foreign body. It has limited identified expressed 'invasive capacity,' although many virulence genes are present [1]. Could such a strain establish itself in the urine and prevent other pathogenic organisms from establishing residence and causing illness? Indeed, pilot studies have suggested that it might be feasible and safe to introduce this strain into the bladder of catheterized patients, with the idea that excluding more-virulent pathogens would result in fewer complications [3, 4].

The article by Darouiche et al. [5] provides further evidence that this "safe" strain of E. coli (strain 83972) lives up to this reputation. After an effort was made to rid the urinary tract of existing bacteria with systemic antimicrobial agents, the bladders of 21 catheterized male patients with spinal cord injury were inoculated 6 times over 3 days via the catheter. In 4 patients, the bladder was successfully colonized for a full year, whereas the bladders of 9 patients were colonized temporarily (mean duration, 3.5 months). With successful colonization, no symptoms were attributed to the presence of this strain during a total of 5.6 years of catheterization. These 13 successfully colonized patients had significantly fewer symptomatic infections (which were presumably due to other infecting pathogens) than did a combined group of 14 patients that included 6 controls who were inoculated with saline and 8 patients whose bladders did not achieve colonization, despite undergoing bladder inoculation.

In earlier studies from these same investigators, data demonstrated that colonization of patients with this E. coli strain resulted in a substantially reduced number of infections and no symptomatic infections during 18.4 years of successful colonization in one study [3] and resulted in 2 infections during 34 patient-years in another study [4]. In no instance did the introduced E. coli cause symptomatic episodes.

From my perspective, as we await the next chapter of this important but slow-moving story, we have more questions than answers. First, these investigators need to solicit multiple groups to contribute to the further development of this strategy, possibly partnering with a commercial interest to speed up the process. We have no shortage of chronically catheterized patients with catheters in our institutions, and if this strain of E. coli or another bioengineered variant could markedly reduce complications of catheterization, patients and their caregivers...
would be most grateful. Studies must be designed well and carefully blinded, because interpreting symptoms in the ne-
urogenic urinary tract is fraught with difficulties. Fever, increased generalized spasticity, and bladder spasms may be
caused by multiple etiologies in this pa-

tient population.

Second, is this strain, indeed, impotent with respect to invasion of the host or
causing an inflammatory host response? Does it stay in the bladder, or does it also
migrate into the upper tracts? Do any renal changes result from chronic infection of
the renal pelvis or other structures? Can the strain be virulent in the obstructed
urinary tract or the immunocompromised host? Can it cause infections at any site
other than the urinary tract? Will bacter-

emia or serious infection ever result in any situation and cause medical legal issues?

Some of us recall the Staphylococcus aureus
502a strain used as a nasal replacement
strategy in the 1970s that failed, because
the inoculated strain also caused disease
[6]. Currently, the medical use of live or-
organisms to exclude other pathogenic mi-
crobes has not made much headway, de-
spite its potential. What kind of evidence
will regulatory agencies require to permit
packaging and distribution of this strain
for use as a prescribed regimen for instil-
lation into urinary tracts? What additional
studies are required to ascertain its safety?
Should the US Food and Drug Adminis-
tration and other regulatory agencies be
involved with study design and analysis?

Third, what routines for inoculation
into the bladder will ensure the more or
less permanent establishment of E. coli
83972 with the least effort and cost? Will
repeated doses be required to maintain
colonization? Can the strain prevent other
strains from invading if they cohabit the
urinary system, or does it need to crowd
out all others to be effective? How will
success of colonization be monitored? Can
we prevent antimicrobial use for purposes
other than eradicating designer E. coli? If
we make the strain more resistant to an-
timicrobials with genetic manipulation, is
there risk that it will transmit these genes
to other pathogens? Are other patients at
any risk for cross-infections?

Fourth, what (if any) undesirable effects
will E. coli 83972 produce in infected
urine? Will there be any new unpleasant
odors emanating from E. coli–infected
urine that is stored in containers or that
has been splashed on surfaces? Can E. coli
83972 be given a gene that might reduce
undesirable urinary odors?

This innovative concept may be a sig-
nificant breakthrough in the management
of the chronically catheterized patient with
a catheter. The multiple pilot studies re-
ported to date are intriguing, but the find-
ings are not absolutely convincing [3–5].
Presumably, this treatment could be ad-
ministered in all situations that require
months or years of urinary drainage, re-
gardless of the etiology of the bladder mal-
function, and, thus, it could be offered to
millions of patients, perhaps resulting in
substantially reduced morbidity and in-
creased financial savings. But we require

a research strategy to be planned and im-
plemented that includes several investiga-
tor groups, regulatory agencies, and per-
haps potential consumers that addresses
all of these questions and others within a
reasonable time frame.

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