Recurrent Multidrug Resistant Urinary Tract Infections in Geriatric Patients

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Four case studies are presented, which suggest the safety and efficacy of methenamine hippurate to treat complicated urinary tract infections in geriatric patients.

Urinary tract infections (UTIs) account for 8.3 million doctor visits, 1 million emergency department (ED) visits, and 100,000 hospitalizations annually, with an estimated cost of $1 billion annually in the U.S.¹ UTIs are the most common bacterial infections found in nursing home residents, accounting for 50% of reported infections in Norwegian nursing homes, 30% to 50% in U.S. nursing homes, and 25% of all infections in the non-institutionalized elderly in the U.S.²⁻⁴ In the geriatric population, UTIs are often found incidentally at the time of hospitalization for other admitting diagnoses, such as mentation changes or falls.³ Asymptomatic pyuria was found in 14.8% of community residents aged ≥ 80 years.⁵ Woodford and colleague found that 37% of geriatric patients admitted through an ED diagnosed with UTIs had no dysuria or urinary frequency.⁶

The incidence of UTIs is higher in the elderly due to genitourinary abnormalities, urolithiasis, dehydration, and diabetes, among other causes. These are considered complicated UTIs, defined as those in the presence of factors that predispose to persistent or relapsing infection, such as foreign bodies (calculi, indwelling catheters), obstruction, renal failure, and urinary retention.⁸

In elderly men, prostate enlargement causes bladder outlet obstruction predisposing them to urinary stasis and UTIs.² UTIs are prone to recur when urinary tract abnormalities persist or treatment ineffectively eradicates resistant bacteria. UTIs are considered recurrent when ≥ 3 occur within 1 year or ≥ 2 occur in a 6-month period. The anticipated recurrence rate of complicated UTIs at 4 to 6 weeks following completion of therapy is 40% to 60%.⁴

Current practice standards recommend not treating asymptomatic UTIs to avoid contributing to bacterial antibiotic resistance.⁹ The frequent use of antibiotics, such as quinolones, which are increasingly inactive against these organisms, contributes to the overgrowth of bacteria in the gastrointestinal tract and their appearance in the genitourinary tract.¹⁰⁻¹¹

Methenamine hippurate, a drug developed 60 years ago, offers an option to the bacterial resistance challenge for select patients with recurrent, multidrug resistant (MDR) UTIs. The action of methenamine is novel—it converts to formaldehyde when it comes in contact with acidic urine. Formaldehyde destroys Gram-positive organisms by lysis of the bacterial cell wall. Gram-negative bacteria are destroyed when formaldehyde denatures enzyme proteins involved in vital metabolic processes.¹² Formaldehyde in dilute solutions has the ability to inhibit cell division, and higher levels are bactericidal.¹³ Exposure to formaldehyde for ≥ 2 hours is necessary to achieve bacteriostatic effects.¹⁴

The European Commission Scientific Committee on Health and Environmental Risk reported that in...
patients receiving up to 4,000 mg/d methenamine for preventive long-term treatment of UTIs, no adverse effects (AEs) were noted (Figure).\textsuperscript{17}

Complicated UTIs in the elderly are difficult to treat due to bacterial resistance. The off-label use of methenamine hippurate for treatment/prophylaxis of MDR-recurrent UTIs is a compelling option, explored further in the following case studies. Four case studies using methenamine for treatment and prevention of recurrent MDR UTIs in geriatric patients are presented.

**TREATING UTI PATIENTS**

**Case Study 1**
A man aged > 89 years, symptomatic with nocturia due to benign prostatic hypertrophy (BPH) with bladder outlet obstruction had 8 symptomatic UTIs over 15 months. His urine culture tested positive for MDR *Providencia stuartia* (resistant to ampicillin, cephalixin, gentamycin, tigecycline, tobramycin and sulfamethizole) and *Staphylococcus haemolyticus* (resistant to ciprofloxacin, nitrofurantoin, and septrin). Postvoid residual urine was identified as the cause for his recurrent UTIs. Self-catheterization was recommended, but the patient declined. Due to his advanced age and preference, surgical intervention was not pursued. His renal function was within normal limits.

Treatment with methenamine hippurate 500 mg bid with 1,000 mg ascorbic acid to acidify the urine was initiated. This reduced dose of 500 mg bid (rather than 1,000 mg bid) was prescribed due to his advanced age and a choice to “err on the side of caution.” Two months later, urinalysis was negative for leukocyte esterase and nitrates, and the growth culture tested negative. Three- and 6-month urinalyses also showed no growth. The patient’s renal function remained stable. He experienced no AEs from the methenamine.

Due to his urinary retention, formaldehyde was able to collect in his bladder for longer than 2 hours, achieving bactericidal levels and effectively preventing recurrence of MDR UTIs.

**Case Study 2**
A man aged > 89 years with BPH and urinary incontinence managed with an external urinary device worn continuously had a history of 4 UTIs within a 6-month period. His renal function was normal with a creatinine clearance of 37 mg/dL. He was diagnosed with a symptomatic UTI cultivating > 100,000 CFU *Proteus mirabilis* (resistant to ciprofloxacin, nitrofurantoin, and septrin).

Due to resistance of the organism to available oral antibiotics, the patient’s desire to avoid hospitalization, and his caregiver’s inability to learn to administer IV antibiotics in the home, methenamine hippurate 500 mg bid was initiated. Within 21 days, the patient’s urinalysis was negative, indicating no bacterial growth. He was treated for 4 months with no recurrence of a UTI. No symptomatic UTIs recurred during the ongoing methenamine treatment.

**Case Study 3**
A man aged > 89 years with end-stage renal disease and a history of bladder cancer declined dialysis, indicating that his goals for care were palliative. He was followed at home by a hospice team. He had 3 recurrent symptomatic MRSA UTIs in a 9-month period (resistant to ciprofloxacin, levofloxacin, penicillin, and oxacillin). The antibiotics the bacteria was sensitive to, nitrofurantoin and septrin, could not be given because his creatinine clearance was merely 8 mg/dL. He was prescribed 500 mg methenamine with 1,000 mg ascorbic acid bid. Within 4 weeks, his urinalysis had changed from > 100,000 CFU to > 50,000 CFU (< 100,000 CFU). One month later with the only treatment the methenamine and ascorbic acid, there was no bacterial growth in the patient’s urine culture. He had no recurrence of a symptomatic UTI while receiving methenamine.

**Case Study 4**
An 89-year-old man with BPH and recurrent MRSA UTIs had 3 hospitalizations within 1 year. He had stage 3 chronic kidney dis-
ease with a creatinine clearance of
43 mg/dL. The patient had a symp-
tomatic UTI > 100,000 CFU MRSA.
He was treated with 500 mg methen-
amine and 1,000 mg ascorbic acid
bid. Urinalysis results 2 months later
revealed the bacterial count had
dropped to the colonization range
(< 50,000 CFU). His urinalysis was
positive for leukocyte esterase with
high white blood cell (WBC) counts,
but it was negative for nitrites. He con-
tinued without recurrent UTIs while
receiving the medication.

**DISCUSSION**

Patients with similar profiles to those
discussed in this report were treated
with less dramatic results. Several
remained free of symptomatic UTIs
with urine cultures showing bacterial
counts in the colonization range of
< 50,000 CFU, as noted in case 4. Fre-
frequently, patients treated with methen-
amine have urinalyses with negative
nitrites, positive leukocyte esterase,
high WBCs, and few bacteria, but cul-
tures show no growth. Some patients
who did not reliably take medications
as prescribed had recurrent symp-
tomatic UTIs. Some had a subsequent
UTI culturing a different organism or
a change in the sensitivity profile of
the same organism. This phenomenon
suggests that formaldehyde disrupts
the manufacture and transmission of
the proteins and enzymes responsible
for bacterial resistance factors.

Freeman and colleagues con-
ducted a prospective study of 249 men with bacteruria followed for
up to 10 years.18 Continuous therapy
with methenamine delayed recur-
rence of bacteruria. Nilsson found
that recurrent UTIs were reduced by
25% with long-term treatment
(> 3 months) with methenamine.19

Bacteria do not develop resistance
to methenamine, which can cause
crystallization in the urine. Daily dos-
ing used in studies ranged from 1 g to
4 g daily.21 Nilsson conducted research
over 16 months with geriatric patients
and found no changes in renal func-
tion or crystallization in urine.19

Severe hepatic impairment is also a
contraindication, as methenamine can
be hydrolyzed to ammonia. Studies
have shown a reduced effectiveness
with lower urinary tract abnormalities,
although those studies administered
the medication for short periods of
time.21 Because the action of the med-
ication relies on ≥ 2 hours of exposure
to urine in the bladder, patients with
indwelling catheters or patients who
urinate frequently experience little
benefit.22 Ideal candidates for methen-
amine are those with urinary reten-
tion and recurrent UTIs.

Although the use of methenamine
has increased in Norway and Sweden
by 24% since 2000, the use of methen-
amine in the U.S. remains low, per-
haps because of conflicting reports in
the literature regarding effectiveness
and use with limited populations (ie,
noncatheterized patients, those able
to retain urine for ≥ 2 hours, and a
creatinine clearance > 50 mg/dL).3

Some health care providers use
methenamine for UTI prophylaxis,
but this practice is less common in the
U.S. than it is in Scandinavian
countries.5 However, no published
studies have explored the action of
methenamine on MRSA, ESBL, and
VRE bacteria or on the enzymes and
proteins that enable and transmit
bacterial resistance factors.

Elderly patients with complicated
recurrent UTIs due to resistant bacte-
ia are often left with no oral antibiotic
options. Costs escalate rapidly when
IV antibiotics are given. Administra-
tion generally requires hospitalization
with close monitoring of renal func-
tion and drug levels and the place-
ment of a PICC or midline IV access.
If there is no caregiver, then hospital-
ization followed by an admission to a
skilled nursing facility is required.

Lee and colleagues concluded that
there is a need for further studies to
explore long-duration therapy with
methenamine.21 No studies have ad-
dressed its use in the geriatric popula-
tion for long-term use of prevention of
recurrent UTIs. No studies have been
done on its use for primary treatment
of MDR UTIs. The benefits of this drug
with a low AE profile and low cost
($60/month for 1 g bid), which has
been proven to reduce the incidence
and/or delay recurrence of UTIs, is
well worth further examination.

**CONCLUSION**

Multiple studies over 60 years have
shown methenamine hippurate to be
a well-tolerated and safe medication.
Little data are available about the use
of this medication in the elderly in the
U.S., despite its wide use in Scandina-
vian countries. Use of methenamine
for MDR UTIs in the geriatric popula-
tion has been shown to be safe and
effective, as presented in these case
studies. Substantial cost savings were
realized with the use of methenamine
in these geriatric patients by reduc-
ing hospitalizations and complications
due to recurrent MDR UTIs. The use
of methenamine for treating MDR
UTIs and the prevention of recurrent
UTIs in the geriatric population war-
rants further clinical use and research.

The very interesting changes
noted in sensitivity of the same bac-
teria in subsequent UTIs in patients
treated with methenamine raises
questions about the action of formal-
dehyde in the bladder on bacterial resis-
tance factors. Given the worldwide
increase in bacterial resistance to cur-
cently available antibiotics, this is a
most compelling action that demands
further study.
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REFERENCES