

### Nitrofurantoin: Preferred Empiric Therapy for Community-Acquired Lower Urinary Tract Infections

*To the Editor:* I read with great interest the article on nitrofurantoin for uncomplicated urinary tract infections (UTIs) by McKinnell et al.<sup>1</sup> Although their study primarily focused on pharmacoeconomics, comparing nitrofurantoin to trimethoprim/sulfamethoxazole (TMP-SMX) and fluoroquinolones, it has important clinical implications.

Nitrofurantoin is an underused antimicrobial for empiric therapy for community-acquired and nosocomial lower UTIs. Among susceptible uropathogens after extensive use worldwide for more than 50 years, there has been virtually no acquired resistance to nitrofurantoin.<sup>2,3</sup> Most physicians are acquainted with the adverse effects of nitrofurantoin but are unfamiliar with its virtues. Nitrofurantoin has a unique mechanism of action by interfering with bacterial growth at 3 different locations in the Krebs cycle. Although approximately 25% of nitrofurantoin is excreted renally, some is eliminated via the gastrointestinal tract. Unlike “high resistance potential” antibiotics, nitrofurantoin does not predispose to resistance.<sup>4</sup> Pharmacokinetically, nitrofurantoin reabsorption is pH dependent and at normal urinary pH (approximately 5.5 pH); nitrofurantoin is preferentially excreted into the lower urinary tract, ie, bladder urine, making it useful to treat lower UTIs.<sup>3,5-7</sup>

Nitrofurantoin is active against most common uropathogens, but most *Proteus* species, *Serratia marcescens*, and *Pseudomonas aeruginosa* are naturally resistant.<sup>4,8</sup> Nitrofurantoin is useful against *Escherichia coli* and *Enterococci*, the most frequent causes of nosocomial lower UTIs, ie, catheter-associated bacteriuria. Nitrofurantoin is also active against most strains of multidrug-resistant gram-negative bacilli, including most extended spectrum  $\beta$  lactamase-producing strains.<sup>8</sup> Nitrofurantoin is also ac-

tive against vancomycin-sensitive enterococci and vancomycin-resistant enterococci.<sup>3,7,8</sup>

During the past 3 decades, I have had extensive experience with nitrofurantoin therapy for nosocomial and community-acquired lower UTIs. Nitrofurantoin, 100 mg orally every 12 hours is well tolerated. The adverse effects of nitrofurantoin are relatively uncommon and benign.<sup>4,8</sup> Occasional nausea may occur but is uncommon with macrocrystalline formulations. In patients with intact renal function, nitrofurantoin urinary concentrations are 50 to 300 mg/mL.<sup>8</sup> With creatinine clearances lower than 30 mL/min, therapeutic urinary concentrations are unlikely to be obtained, and therapeutic failure may result.<sup>4,8</sup> For this reason, nitrofurantoin should be avoided in patients with a creatinine clearance lower than 30 mL/min.<sup>7,8</sup> Acute toxicity is limited to acute/reversible migratory pulmonary infiltrates/eosinophilia. Long-term nitrofurantoin toxicity includes peripheral neuropathy, interstitial lung disease, or hepatotoxicity, which may occur in patients treated long term who have chronic renal insufficiency.<sup>6,8</sup> Nitrofurantoin has advantages over TMP-SMX and fluoroquinolones for initial empiric therapy of community-acquired and nosocomial lower UTIs. Against gram-negative bacilli uropathogens, nitrofurantoin has a “low resistance potential” vs the “high resistance potential” of TMP-SMX and ciprofloxacin. Unlike TMP-SMX and fluoroquinolones, nitrofurantoin has activity against vancomycin-resistant enterococci<sup>3,8</sup> (Table).

In my experience-based opinion, nitrofurantoin should be the preferred empiric therapy for community-acquired and nosocomial lower UTIs. Nitrofurantoin has remained effective after more than 50 years of extensive use worldwide with essentially no resistance, and for initial empiric therapy for uncomplicated community-acquired or nosocomial UTIs, nitrofurantoin is an ideal antibiotic. If urine cultures are positive for *Proteus* species, *S marcescens*, or *P aeruginosa*, an

TABLE. Antibiotic Activities Against Selected Gram-Negative and Gram-Positive Uropathogens<sup>a</sup>

Uropathogen	TMP-SMX	Ciprofloxacin	Levofloxacin	Nitrofurantoin
<i>Klebsiella pneumoniae</i> <sup>b</sup>	3	2	2	2
<i>Enterobacter</i> species <sup>b</sup>	2	2	2	2
<i>Escherichia coli</i> <sup>b</sup>	1	1	1	1
<i>Proteus</i> species	1	1	1	0
<i>Serratia marcescens</i>	2	2	2	2
<i>Pseudomonas aeruginosa</i>	1	2	1	0
VSE	0	3	2	1
VRE	0	0	0	1

<sup>a</sup> 0 = little/no activity; 3 = some activity; 2 = good activity; 1 = high activity; TMP-SMX = trimethoprim-sulfamethoxazole; VRE = vancomycin-resistant enterococci; VSE = vancomycin-sensitive enterococci.

<sup>b</sup> Including multidrug-resistant strains.

Adapted from Cunha BA. *Antibiotic Essentials*. 10th ed. Sudbury, MA: Jones & Bartlett; 2011.

alternate agent should be selected. I agree with the authors that nitrofurantoin should be the preferred antibiotic for the initial empiric treatment of community-acquired lower UTIs.

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doi:10.4065/mcp.2011.0411

*In reply:* We appreciate Dr Cunha's correspondence regarding the use of nitrofurantoin for the treatment of urinary tract infections (UTIs). We agree that nitrofurantoin should have a major contemporary role in outpatient treatment of uncomplicated UTIs in the United States and worldwide.<sup>1</sup> Dr Cunha noted one known mechanism of action of nitrofurantoin; we add that the mechanism of bactericidal activity of nitrofurantoin remains unclear and that other mechanisms, including bacterial DNA damage and inhibition of ribosomal translation, may play a role.<sup>2,3</sup>

The renal excretion of nitrofurantoin that Dr Cunha quotes is lower than that in other reports.<sup>4-6</sup> We concur that nitrofurantoin use is relatively contraindicated in patients with renal insufficiency. The urinary recovery of nitrofurantoin is linearly related to creatinine clearance and may not achieve therapeutic concentrations in patients with renal insufficiency.<sup>6</sup> Experts suggest that nitrofurantoin

be avoided in patients with a glomerular filtration rate lower than 60 mL/min,<sup>7</sup> a threshold different from the creatinine clearance of lower than 30 mL/min mentioned by Dr Cunha.

As far as the statement that nitrofurantoin may be a useful agent in the hospital setting, we agree that it may have a role, especially with the increasing incidence of UTIs caused by multidrug-resistant organisms. Of note, the role of nitrofurantoin for nosocomial UTIs is poorly studied.<sup>8</sup> We also caution that nitrofurantoin resistance among uropathogens that cause catheter-associated UTIs has been reported to be as high as 29%, thus limiting its role as empiric therapy.<sup>9</sup> We encourage publications on clinical experience, or ideally prospective study, with nitrofurantoin in this setting because such data will be a welcome and important addition to the clinical literature.

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doi:10.4065/mcp.2011.0469

### The “Spiked Helmet” Sign: A New Electrocardiographic Marker of Critical Illness and High Risk of Death

*To the Editor:* In critically ill patients, ST-segment elevation myocardial infarction (STEMI) is a relatively common finding on the electrocardiogram (ECG). However, many such patients do not have STEMI.<sup>1</sup> One of the rare causes of ST-segment elevation is artifact. The purpose of this case series is to present a new, unique pattern of apparent STEMI whose presence was found to be associated with critical illness and very high risk of in-hospital death.

During the routine interpretation of ECGs of hospitalized patients, we collected 8 cases in which the ECG showed apparent ST-segment elevation but with the upward shift starting before the onset of the QRS complex (Figure). In each case, the ECG showed a dome-and-spike pattern, giving the appearance of Pickelhaube, the German military spiked helmet introduced in 1842 by Friedrich Wilhelm IV, King of Prussia (Figure).

We were actively involved in the care of the most recent case, case No. 8 (Table). A 58-year-old woman was hospitalized for diarrhea, nausea, vomiting, and dehydration. On hospital day 2, she experienced severe abdominal pain but no chest pain. She had tachycardia, tachypnea, and diffuse abdominal tenderness. Telemetry suggested ST-segment elevation, and a subsequent 12-lead ECG with computer interpretation indicated inferior STEMI. Careful analysis of the ECG revealed that the upward baseline shift started

before the onset of the QRS complex (Figure, last strip), which would be inconsistent with STEMI. Furthermore, an emergent echocardiogram demonstrated no wall motion abnormality, and cardiac serum markers were negative. A repeat ECG 2 hours later showed no ST-segment elevation. Within 12 hours, the patient had evidence of acute abdomen. Emergent laparotomy revealed perforated bowel with extensive bowel necrosis. Despite aggressive surgical and medical management, the patient died 24 hours after the ECG was obtained that exhibited the “spiked helmet” sign.

We think that the pseudo-ST segment elevation possibly occurred at the time and may have been a reflection of the bowel perforation. On the basis of this experience, we decided to review all other cases in our collection in which the ECG showed a similar spiked helmet pattern and found the following similarities (Table). First, each patient had critical noncardiac illness. Second, despite the ECG interpretation software indicating STEMI, acute MI was uniformly ruled out by cardiac serum markers. Third, the spiked helmet sign was present exclusively in the inferior leads (II, III, aVF). Fourth, 7 of the 8 patients had ECGs recorded before and/or after the index ECG, but none showed ST elevation. Finally, 6 of the 8 patients died 1 to 10 days after the index ECG (mean, 5.5 days), corresponding to a mortality of 75% (95% confidence interval, 34.9%-96.8%; SAS, version 9.2; Cary, NC). Only 2 patients were discharged from the hospital, both debilitated—one to a rehabilitation center and one to a skilled nursing facility.

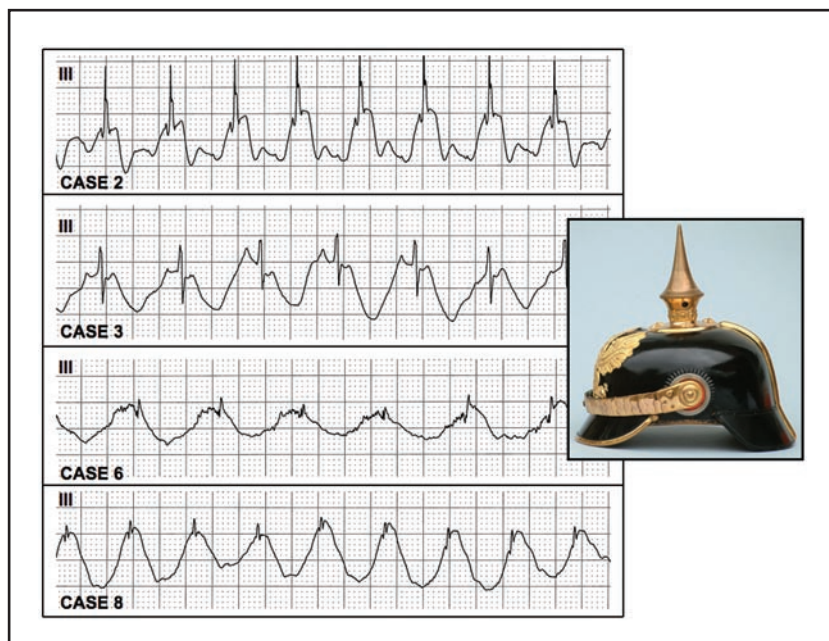


FIGURE. Left, representative electrocardiograms of 4 patients showing the “spiked helmet” sign. Right, Pickelhaube, the German military spiked helmet. Note the similarity of the electrocardiogram waveforms in lead III to the shape of the spiked helmet.

TABLE. Clinical and Electrocardiographic Characteristics of Patients With the “Spiked Helmet” Sign<sup>a</sup>

Case No./age (y)/sex	Clinical diagnoses	Interventions	ECG leads with the “spiked helmet” sign	Width of pseudo-ST elevation (mm/ms) <sup>b</sup>	Height of pseudo-ST elevation (mm/mV) <sup>b</sup>	Admission to ECG (d)	ECG to death (d)
1/46/M	Pneumonia, sepsis, hypothermia, DKA, ARF, respiratory failure	I/MV, RHC, pressors, CPR	II, III	8.5/340	5.0/0.5	0	4.5
2/54/F	ESRD, PAD, cellulitis, sepsis	I/MV, RHC, hemodialysis, pressors, CPR	II, III, aVF	6.5/260	5.8/0.58	15	2
3/71/F	ALS, respiratory failure, altered mental status, fever, diarrhea, VAP, empyema	MV, chest tube	II, III, aVF	8.5/340	4.0/0.4	7	NA
4/22/M	Trauma, sepsis, cardiac tamponade, anoxic brain damage, seizures	I/MV, pericardiocentesis, chest tube, pressors, CPR	II, III, aVF	8.0/320	3.0/0.3	4	NA
5/44/M	NIDCM, cardiac arrest, anoxic brain injury, sepsis, DVT, ARF, seizures	I/MV, pressors, CPR	II	14.0/560	7.0/0.7	0	8.5
6/66/M	SDH, SAH, anoxic brain damage	I/MV, craniotomy	II, III, aVF	8.5/340	3.5/0.35	0	10
7/55/F	AIDS, PCP, respiratory failure, pneumothorax	I/MV, chest tube	III, aVF	8.5/340	1.5/0.15	4	7
8/58/F	Bowel perforation, bowel ischemia, sepsis, shock	I/MV, pressors, abdominal surgery, drain	II, III, aVF	8.5/340	9.0/0.9	2	1

<sup>a</sup> ALS = amyotrophic lateral sclerosis; ARF = acute renal failure; CPR = cardiopulmonary resuscitation; DKA = diabetic ketoacidosis; DVT = deep venous thrombosis; ECG = electrocardiogram; ESRD = end-stage renal disease; I/MV = intubation and mechanical ventilation; MV = mechanical ventilation; NA = not applicable (patient was alive when discharged from the hospital); NIDCM = nonischemic dilated cardiomyopathy; PAD = peripheral arterial disease; PCP = *Pneumocystis carinii* pneumonia; RHC = right heart catheterization; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; VAP = ventilator-associated pneumonia.

<sup>b</sup> Measured in the lead exhibiting the tallest pseudo-ST elevation; averaged from 5 consecutive cycles.

The exact mechanism of the spiked helmet ECG pattern and its association with critical illness is uncertain, but several observations point to the possible role of the diaphragm. Certain pathological conditions can rarely result in repetitive contraction of the diaphragm that is in concert with the cardiac cycle.<sup>2,3</sup> Postulated mechanisms of this pulsatile diaphragmatic motion include direct stimulation of the diaphragm by the inferior wall of the left ventricle or triggering of the left leaf of the diaphragm by the left phrenic nerve.<sup>2,3</sup> Such diaphragmatic contractions may result in alteration of the ST segment, which is best seen in the inferior leads.<sup>2,3</sup> A possible mechanism to explain pseudo-ST segment elevation is repetitive epidermal stretch in association with nearby pulsatile flow or due to an acute rise in the intrathoracic or intra-abdominal pressure.<sup>4,5</sup> From this perspective, it may be of significance that 7 of the 8 patients in our series were intubated and undergoing mechanical ventilation at the time of the ECG recording, and 4 of 8 had documented free air, fluid, or mechanical tubes and drains in either the thorax or the abdomen (Table).

The spiked helmet sign is a potential novel ECG marker of a very high risk of impending death, but the prevalence, mechanism, and clinical applicability remain uncertain at this time. Repetitive signals in the ECG that are not generated by cardiac depolarization or repolarization have previously been shown to provide important clues to

patients' clinical conditions and guidance on their treatment.<sup>6</sup> Further experience is needed to determine whether the spiked helmet sign will eventually change clinical management or just remain an electric curiosity.

We thank Nicole M. Fesel, RN, for her assistance in data collection.

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doi:10.4065/mcp.2011.0647



## Gaining Insights Into Chronic Natural Killer Cell Leukemias Through Extensive Characterization of an Individual Case

*To the Editor:* Chronic lymphoproliferative disorder of natural killer cells (CLPD-NK) is a recently recognized provisional entity characterized by abnormal peripheral blood natural killer (NK) cell expansions with associated cytopenias.<sup>1</sup>

We report a 46-year-old man who presented to his local physician with fatigue, lethargy, and unexplained weight loss associated with mild to moderate pancytopenia and modest lymphocytosis consisting of cells with small round nuclei and abundant granulated cytoplasm. Physical and radiologic examinations revealed prominent splenomegaly. Bone marrow examination and splenectomy revealed the marrow interstitium and splenic red pulp to be infiltrated by lymphocytes strongly positive for CD2, TIA-1, and granzyme B; variably positive for CD56; and negative for CD3, CD5, CD7, and CD8.

Peripheral blood flow cytometry revealed that 90% of the lymphocytes were brightly CD16 positive; CD3 negative NK cells with abnormal loss of CD7, NKp46 (CD335), and KIRs (CD158a, CD158b, and CD158e); and diminished CD56 and CD57 expression. The NK cells strongly expressed activation markers, NKp80, CD94/NKG2a heterodimer, and NKG2D (CD314). The plasma level of the NK cell activating cytokine interleukin (IL) 12 was more than 5 times above the upper limit of normal; the levels of interferon  $\gamma$ , IL-2, and IL-15 were within normal limits.

In vitro, the leukemic cells had abnormally high levels of cytotoxicity through the activating receptors CD16,

NKG2D (CD314), and NKp80 in the absence of normally requisite cellular priming or exogenous cytokines (Figure). This cytotoxicity was completely abrogated by simultaneous ligation of the inhibitory CD94/NKG2A receptor complex. To measure their cytolytic activity against potential physiologic targets, cytotoxicity assays were performed using freshly isolated normal human neutrophils as the cellular target. In these assays, the leukemic NK cells demonstrated more than 5-fold higher levels of neutrophil cytotoxicity than normal activated NK cell controls (Figure).

After splenectomy the patient had a period of symptomatic improvement followed by disease progression requiring prednisone and methotrexate therapy. At last follow-up, 18 months after splenectomy, the patient was asymptomatic while receiving continued methotrexate therapy.

The features in this case, including the prolonged course, associated cytopenias and infection, lack of Epstein-Barr virus positivity, and loss of NKp46, are diagnostic of CLPD-NK.<sup>1,2</sup> The loss of NKp46 seen in CLPD-NK is intriguing when considering the similar entity T-cell large granular lymphocytic leukemia because studies suggest that it is derived from NKp46-positive T cells highly responsive to IL-15.<sup>3</sup> Our serologic, phenotypic, and functional studies indicate that the leukemic NK cells are in a persistent, highly activated state with an abnormal capacity to mediate cell lysis through ligation of either NKG2D alone or NKp80 not associated with commensurate loss of responsiveness to inhibitory signals.<sup>4</sup> Importantly, the potent ability of the leukemic cells to lyse normal neutrophils provides strong evidence that direct cytotoxicity is a cause of the disease-associated cytopenias; this activity may be mediated by NKp80 because its ligand, AICL, is expressed

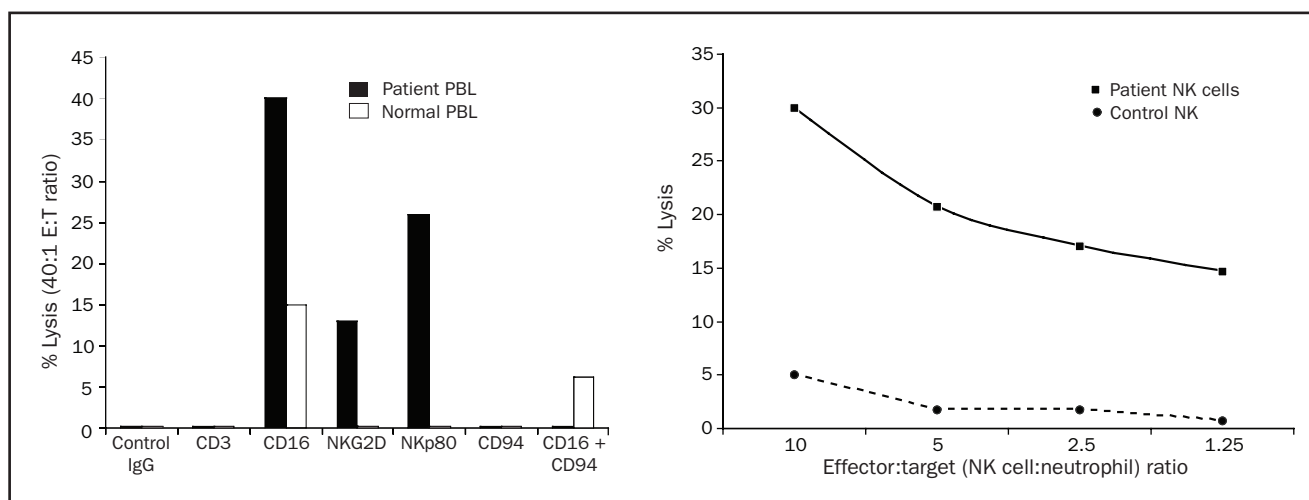


FIGURE. Cytotoxic activity of the leukemic natural killer (NK) cells. Left, The ability of freshly isolated patient peripheral blood lymphocytes (PBLs) to lyse target cells through receptor ligation was measured and compared to freshly isolated normal PBLs (reverse antibody-dependent cellular cytotoxicity, data shown for 40:1 effector:target [E:T] ratio). The leukemic PBLs exhibit supranormal levels of cytotoxic activity when activated through CD16, NKG2D, or NKp80. The activity mediated by NKp80 cross-linking is particularly unusual because these cells lacked detectable NKp46 expression. Furthermore, the strong CD16-mediated activation in the leukemic PBL is completely abrogated by coligation of the highly expressed inhibitory CD94/NKG2A heterodimer. Right, The purified leukemic NK cells also show abnormally high levels of direct neutrophil cytotoxicity when compared to activated normal human NK cells over a wide range of NK cell-to-neutrophil (E:T) ratios.

on myeloid cells.<sup>5</sup> Our observations support the hypothesis that CLPD-NK is a disorder of activated NK cells and that inappropriate cellular cytotoxicity may be responsible for many of the clinicopathologic features. Hopefully, these insights will provide the opportunity to further understand these rare NK cell leukemias and lead to therapies targeted at specific cellular pathways.

We acknowledge Xiangyang Dong, PhD, Roshini S. Abraham, PhD, Melissa R. Snyder, PhD, Grzegorz S. Nowakowski, MD, Daniel D. Billadeau, PhD, and Renee A. Schoon, BS, for their assistance in the case evaluation and the patient for his dedication and generosity.

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doi:10.4065/mcp.2011.0637

## CORRECTION

**Incorrect data in table:** In the article entitled “MAP0004, Orally Inhaled Dihydroergotamine for Acute Treatment of Migraine: Efficacy of Early and Late Treatments,” published in the October 2011 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2011;86(10):948-955), Table 1, on page 953, contains some incorrect information in the entry “Percent of predicted FEV<sub>1</sub>, mean (SD).” The data in bold typeface are corrected entries.

TABLE 1. Patient Baseline Demographic Features

	mITT population patients	
	MAP0004 (n=385)	Placebo (n=386)
Percent of predicted FEV <sub>1</sub> , mean (SD)		
Overall	91.8 (11.9)	92.8 (12.5)
Treated in ≤1 h	<b>91.5 (11.3)</b>	<b>94.0 (12.9)</b>
Treated >1 h to ≤4 h	<b>92.0 (12.1)</b>	<b>92.2 (12.7)</b>
Treated >4 h to ≤8 h	<b>93.0 (11.0)</b>	<b>91.9 (10.6)</b>
Treated >8 h	<b>90.0 (13.8)</b>	<b>92.7 (12.8)</b>

FEV<sub>1</sub> = forced expiratory volume in 1 second; mITT = modified intent-to-treat.

doi:10.4065/mcp.2011.0734