Hospital Resources for Pandemic Influenza

To the Editor: In their November 2007 article, Pandemic Influenza and Hospital Resources, Nap et al. evaluated hospital resources for pandemic influenza in the northern part of the Netherlands (*1*). Their results can be compared with those that I have described for the combined suburban communities of Roswell and Alpharetta, Georgia, USA (*2*). The Netherlands evaluation assumed that antiviral drugs will be available and will reduce hospitalizations by 50% and deaths by 30%. In view of the uncertainty of effective antiviral drugs and timeliness of vaccines, I did not estimate their effects. Nevertheless, several issues warrant comparison.

The plan for the Netherlands has no provisions for urgent care, i.e., parenteral fluids or antimicrobial drugs that are administered to ambulatory patients who are not hospitalized. Nap et al. may not perceive a need for enough beds to handle surge capacity. Allowing for 30% of beds to be used for patients with conditions other than influenza, they report a maximum availability of 232 beds per 100,000 population for pandemic influenza patients, and they estimate use of 72 beds per 100,000 in the pandemic model. In contrast, a maximum of 47 beds per 100,000 are available in Roswell/Alpharetta. Availability of beds in intensive care units, however, is identical for both regions, at 8 beds per 100,000 population.

The Netherlands plan calls for intensified treatment evaluation in 48 hours to withdraw care from patients who have little chance for recovery. Because most patients can be expected to have pneumonia and 2-organ failure (on average), a 50% mortality rate can be expected. In US hospitals, withdrawing care is difficult, even if mortality rates are expected to be 75% or 90% during acute illness with organ failure.

The pandemic influenza resource evaluation from the northern part of the Netherlands provides a useful contrast with at least 1 US hospital. The dramatic difference in bed availability highlights the potential challenges involved in local planning. The surge capacity limits in Roswell/Alpharetta led us to consider an alternative infusion center to provide care during an influenza pandemic.

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References

1. Nap RE, Andriessen MPHM, Meessen NEL, van der Werf TS. Pandemic influenza and hospital resources. Emerg Infect Dis. 2007;13:1714–9.
2. Dailey MP. Pandemic influenza and community medical care. South Med J. In press.

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Multidrug-Resistant *Acinetobacter baumannii* Osteomyelitis from Iraq

To the Editor: *Acinetobacter baumannii* identified in military settings is commonly multidrug resistant (MDR) (*1–3*). Tigecycline displays *A. baumannii* activity, but clinical experience is limited. We report a case of probable osteomyelitis caused by MDR *A. baumannii* and treated with tigecycline.

A 55-year-old man was transporting soldiers in Iraq when he sustained a grenade injury, in which material entered his anterior thigh and created a large posterolateral hip exit wound and an open left subtrochanteric femur fracture. He was flown to Germany; his wound was debrided, and the fracture was stabilized with an external fixator along with pins to his ilium and proximal and distal femur. A wound vacuum covered the exposed bones within the large soft tissue defect. He was stable upon transfer to our hospital 14 days after the injury; leukocyte count was 16,000/μL (reference range 4.5–11,000/μL), and erythrocyte sedimentation rate (ESR) was 44 mm/h (reference range 0–19 mm/h); blood cultures were not obtained. Plain radiographs showed an open femur fracture with gas in the soft tissue, shrapnel, and a gross deformity of the left iliac wing. ^{111}Indium-labeled leukocyte imaging confirmed increased activity in the left acetabulum, femoral neck, and surrounding soft tissue. Two days after his arrival, the external fixator (except for 1 pin in the distal shaft and 1 in the proximal femur) was removed, and an open reduction and internal fixation (ORIF) of the femur was performed. A cephalomedullary femoral rod and hip screw and 60 tobramycin-impregnated beads were placed into the hip joint; a wound vacuum was placed over the defect. A deep sample of the iliac wing was obtained, ground into a homogenate, placed aseptically on media, and observed for microbial growth; both coagulase-negative *Staphylococcus* and gram-negative rods grew in 1 culture. Both were considered pathogens of probable osteomyelitis based on exposed periosteum. Treatment with vancomycin plus ciprofloxacin was begun. After the gram-negative rods were identified as MDR *A. baumannii*, tigecycline (MIC 1.5) was substituted for ciprofloxacin (MIC>2). *A. baumannii* was susceptible to tobramycin (MIC≤2), intermediate to imipenem (MIC 8), and resistant to

all other agents tested (Microscan, Dade Behring Company, Deerfield, IL, USA). Tigecycline susceptibility was performed by Etest (AB Biodisk, Solna, Sweden); breakpoints were inferred from available literature for *Enterobacteriaceae* (≤2.0 is susceptible) as no current Clinical Laboratory Standards Institute breakpoints are established (*4*). Susceptibility testing for *Staphylococcus* spp. was not performed; tigecycline's role in treating the staphylococci in this setting was not determined because vancomycin was also used.

Postoperatively, leukocyte count returned to normal, wound drainage decreased, and a computed tomographic scan showed appropriate femur alignment with progressive heterotopic bone in the ilium. The patient was transferred to our rehabilitation facility and continued on vancomycin and tigecycline. Two weeks after the ORIF (hospital day 38), the wound vacuum was removed, a split-thickness skin graft was placed, and the patient was discharged. He returned to our infectious diseases clinic 2 weeks later; ESR was 12; tigecycline and vancomycin were stopped after 43 days. The probable osteomyelitis of the femur and ilium was resolved by standard clinical and radiologic parameters.

Tigecycline has displayed activity against many MDR pathogens, including *A. baumannii* in vitro (*4*), although recent investigations have demonstrated resistance and inconsistent susceptibility patterns (*5*). Clinical management of *A. baumannii* bone infections in humans has not been well established. In an experimental animal model of methicillin-resistant *S. aureus,* tigecycline showed adequate bone concentration with microbial clearance in 90% and 100% of patients who received tigecycline and tigecycline plus rifampin, respectively (*6*). This suggests that tigecycline may have also been useful for the coagulase-negative staphylococci identified in this patient and could have been considered as the sole treatment agent.

Tigecycline concentration in bone was also evaluated in an experimental rat model and a single-dose human study (*7*,*8*). The rat model showed an area under the curve in bone ≈250× higher than plasma (*7*). The investigation in humans could not duplicate these results; the discrepancy was attributed to either tight binding of tigecycline to bone or poor extraction methods (*8*). The testing method used in previous animal models was recently adapted for human use and has suggested increased sensitivity (*9*). An assessment of human bone concentrations after multiple tigecycline doses may be necessary to determine the potential role in osteomyelitis management.

Tobramycin bone and surrounding tissue concentrations have been demonstrated after tobramycin-impregnated beads were placed in animals and humans with open fractures or chronic osteomyelitis (*10*). The role of tobramycin beads is not established for osteomyelitis, but use is common. Their contribution to this patient's outcome is difficult to assess because *A. baumannii* was also susceptible to tobramycin.

Cases of *A. baumannii* osteomyelitis have been documented recently, but isolates were susceptible to other agents; none were treated with tigecycline (*3*). The role of tigecycline for osteomyelitis with MDR *A. baumannii* requires further study.

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References

1. Centers for Disease Control and Prevention. *Acinetobacter baumannii* infections among patients at military medical facilities treating injured U.S. service members, 2002–2004. MMWR Morb Mortal Wkly Rep. 2004;53:1063–6.
2. Hujer KM, Hujer AM, Hulten EA, Bajaksouzian S, Adams JM, Donskey CJ, et al. Multi-drug resistant *Acinetobacter* spp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center: analysis of antibiotic resistance genes. Antimicrob Agents Chemother. 2006;50:4114–23.
3. Davis KA, Moran KA, McAllister CK, Gray PJ. Multidrug-resistant *Acinetobacter* extremity infections in soldiers. Emerg Infect Dis. 2005;11:1218–24.
4. Waites KB, Duffy LB, Dowzicky MJ. Antimicrobial susceptibility among pathogens collected from hospitalized patients in the United States and in vitro activity of tigecycline, a new glycylcycline antimicrobial. Antimicrob Agents Chemother. 2006;50:3479–84.
5. Navon-Venezia S, Leavitt A, Carmeli Y. High tigecycline resistance in multidrug-resistant *Acinetobacter baumannii.* J Antimicrob Chemother. 2007;59:772–4.
6. Yin LY, Lazzarini L, Li F, Stevens CM, Calhoun JH. Comparative evaluation of tigecycline and vancomycin, with and without rifampicin, in the treatment of methicillin-resistant *Staphylococcus aureus* experimental osteomyelitis in a rabbit model. J Antimicrob Chemother. 2005;55:995–1002.
7. Tombs NL. Tissue distribution of GAR-936, a broad spectrum antibiotic in male rats. In: Program and abstracts of the Thirty-ninth Interscience Conference on Antimicrobial Agents and Chemotherapy. 1999 Sep 26–29 (San Francisco). Washington: American Society for Microbiology; 1999. p. 413.
8. Rodvold KA, Gotfried MH, Cwik M, Korth-Bradley JM, Dukart G, Ellis-Grosse EJ. Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. J Antimicrob Chemother. 2006;58:1221–9.
9. Ji AJ, Saunders P, Amorushi P, Wadgaonkar ND, Leal M, Fluhler EN. A sensitive human bone assay for quantification of tigecycline using LC/MS/MS. In: Program and abstracts of the Forty-sixth Interscience Conference on Antimicrobial Agents and Chemotherapy. 2006 Sept 17–20 (San Francisco). Washington: American Society for Microbiology; 2006. p. 1952.

10. Wininger DA, Fass RJ. Antibiotic cement and beads for orthopedic infections. Antimicrob Agents Chemother. 1996;40: 2675–9.

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Dengue Virus, Nepal

To the Editor: *Dengue virus* belongs to the genus *Flavivirus*, family *Flaviviridae*. It has 4 serotypes: dengue virus type 1 (DENV-1), dengue virus type 2 (DENV-2), dengue virus type 3 (DENV-3), and dengue virus type 4 (DENV-4). Dengue virus is maintained in a cycle between humans and *Aedes aegypti*, domestic day-biting mosquitoes. Dengue virus induces clinical illness, which ranges from a nonspecific viral syndrome (dengue fever [DF]) to severe and fatal hemorrhagic disease (dengue hemorrhagic fever [DHF]). DF/DHF occurs primarily in tropical and subtropical areas of the world. Domestic dengue virus infection occurs in >100 countries; >2.5 billion persons live in these areas. Approximately 100 million cases of DF, 500,000 cases of DHF, and several thousand deaths occur annually worldwide (*1*). During the past decades, dengue virus has emerged in southern Asia; DF/DHF epidemics have occurred in Bhutan, India, Maldives, Bangladesh, and Pakistan (*2–4*).

From August through November 2006, the number of febrile patients increased in 4 major hospitals in the Terai region of Nepal: Nepalgunj Medical College, Bheri Zonal Hospital in Nepalgunj, Tribhuban Hospital in Dang, and Narayani subregional hospital in Birgunj. Patients with severe symptoms were referred to Sukraraj Tropical and Infectious Disease Hospital, Kathmandu, for diagnosis and treatment. The clinical features in most patients were consistent with signs of DF, but some patients showed signs (high fever, rash, ecchymosis, epistaxis, positive tourniquet test, liver dysfunction, and thrombocytopenia [platelet count <100,000/mm^3]) consistent with the World Health Organization (WHO) definition of DHF. Ascites and plural effusion developed in 2 patients. Blood specimens were collected from all patients at the time of admission to the local hospitals. Particle agglutination (PA) assay (Pentax Ltd, Tokyo, Japan) (*5*) and immunoglobulin (Ig) M–capture ELISA (Dengue/JE IgM Combo ELISA kit, Panbio Ltd, Brisbane, Queensland, Australia) were performed. Dengue virus–specific IgM was detected in 11 patients who had fever, headache, and rash (Table). Each of these patients had negative

Table. Clinical and laboratory data for 11 patients admitted to hospitals and diagnosed with dengue fever or dengue hemorrhagic fever, Nepal, 2006*

Patient age, y/Sex	Month admitted	Location	Initial diagnosis	Travel history	Clinical signs and symptoms	Selected laboratory and other test results
20/M	Sep	Kathmandu	DF	Yes	Fever, headache, nausea	Hb 15.4 g/dL; TLC 10,500/mm^3; Plt 185,000/mm^3; blood culture for salmonellae negative; ALT 38 IU/L
27/F	Sep	Bardiya	Viral fever	No	Fever, headache, vomiting	TLC 5,600/mm^3; blood culture for salmonellae negative
3/M	Sep	Salayan	Encephalitis	No	Fever, vomiting, convulsions	Widal negative; TLC 4,700/mm^3
13/M	Oct	Sindhuli	Typhoid fever	No	Fever, headache	Widal negative; TLC 4,500/mm^3; blood culture for salmonellae negative; *Brucella* antigen negative; chest radiograph normal
22/M	Oct	Birgunj	DHF	No	Fever, headache, vomiting, ascites	Bil 0.8 mg/dL; ALT 80 IU/L; Plt 22,000/mm^3; chest radiograph normal
55/F	Oct	Dang	DF	No	Fever, headache, muscular pain	Plt 51,000/mm^3; TLC 7,600/mm^3; MP negative; ESR 20 mm/h; Bil 0.7 mg/dL
22/F	Oct	Birgunj	Viral fever	No	Fever, headache, body ache	*Brucella* negative; Widal negative; TLC 5,600/mm^3
13/M	Nov	Dang	DF	No	Fever, headache, rashes	Plt 95,000/mm^3; TLC 4,700/mm^3; Hb 13.1 g%; Bil 0.8mg/dL; ALT 26 IU/L
35/F	Nov	Birgunj	DHF	No	Fever, headache, bruises; tourniquet: positive	Bil 0.81mg/dL; Plt 31,000/mm^3; PT 2 min 30 s (control 14)
40/M	Nov	Birgunj	DF	No	Fever, headache, rashes	ALT 127IU/L; Plt 110,000 /mm^3; PCV 38.8%;TLC 5,500/mm^3; ultrasonography liver size, 16.8 cm
42/M	Nov	Dang	DF	No	Fever, headache, rashes	Bil 0.7 mg/dL; Widal test negative; TLC 6,800/mm^3; Plt 164,000/mm^3

*Blood specimens were collected at time of hospital admission. Diagnosis was confirmed by using immunoglobulin M–capture ELISA. DF, dengue fever; Hb, hemoglobulin;TLC, total leukocyte count; Plt, platelets; ALT, alanine aminotransferase; DHF, dengue hemorrhagic fever Bil, bilirubin; MP, malaria parasites; ESR, erythrocyte sedimentation rate; PT, prothrombin time; PCV, packed cell volume.