Decolonize Carriers of *S. aureus* Within 24 Hours

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WASHINGTON — Identifying newly admitted patients who are colonized with *Staphylococcus aureus* and beginning decolonization within the first 24 hours can reduce nosocomial infections by almost two-thirds, according to the results of a randomized study of more than 900 patients.

The occurrence of nosocomial *S. aureus* infection in patients at risk for such infections "can be reduced by almost 60% if carriers are treated with mupirocin and chlorhexidine within 24 hours of admission," Dr. Lonneke Bode said at the jointly held annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the annual meeting of the Infectious Diseases Society of America.

In the trial, Dr. Bode and her colleagues evaluated whether the identification of *S. aureus* carriers by using real-time polymerase chain reaction (PCR) on nasal specimens, followed by prompt treatment with mupirocin nasal ointment and chlorhexidine gluconate medicated soap, reduced the risk of nosocomial *S. aureus* infection in carriers.

Several earlier studies looked at the decolonization of newly admitted patients, but the results to date have been mixed. "Our study differed from previous studies in several aspects," noted Dr. Bode of the department of medical microbiology and infectious diseases at Erasmus Medical Centre, Rotterdam, the Netherlands.

First, they targeted only nasal *S. aureus* carriers for intervention. Second, they assessed carriage using real-time PCR on the day of admission, allowing decolonization of carriers to be started within 24 hours of admission. Third, they aimed to eradicate *S. aureus* carriage not only from the nose but also from the skin. This was accomplished by using twice-daily intranasal mupirocin in combination with daily total

body washes using chlorhexidine soap for 5 days. Last, recolonization of patients with extended hospital stays was prevented by repeating this procedure at weeks 3 and 6.

The trial was conducted at three university hospitals and two general hospitals in the Netherlands. They included patients from wards predetermined to have a high incidence of *S. aureus* nosocomial infections. Immediately on admission, a nasal swab was collected and assessed by PCR. A total of 6,771 patients was assessed between October 2005 and June 2007.

Patients who were positive for *S. aureus* were randomized to the intervention or to placebo nasal treatment and soap. Intervention or placebo was started within 24 hours of admission, in patients with an expected length of stay of at least 4 days. Exclusion criteria included *S. aureus* infection at the time of randomization and the use of mupirocin in the preceding 4 weeks. Patients were followed for up to 6 weeks after discharge. Nosocomial infections were defined by Centers for Disease Control and Prevention criteria.

Nosocomial *S. aureus* infection in patients at risk 'can be reduced by almost 60% if carriers are treated … within 24 hours of admission.'

In all, 917 patients were randomized—504 to the intervention and 413 to placebo. The *S. aureus* infection rate was 3.4% in the intervention group and 7.7% in the placebo group, a difference that was statistically significant. This resulted in a relative risk of infection of 0.42 with the intervention.

Though most of the infections were endogenous, the number of endogenous infections was significantly lower in the intervention group (2%) than in the placebo group (6%). The relative risk of endogenous infection with the intervention was 0.39.

Surgical site infections also were significantly less common in the intervention group (2%) than in the placebo group (7%), for a relative risk of 0.30.

Although there was no significant difference between the two groups in terms of all-cause mortality, the mean length of stay was significantly shorter for the intervention group (12 days), compared with the placebo group (14 days).

Dr. Bode did not report whether she had any potential conflicts of interest. ■

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Hemorrhage

The incidence of major hemorrhagic complications during Lovenox treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with Lovenox Injection [see Tables 2 to 7].

Table 2
Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

	Dosing Regimen	
	Lovenox	Heparin
Indications	40 mg q.d. SC	5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

Table 3
Major Bleeding Episodes Following Hip or Knee Replacement Surgery[1]

	Dosing Regimen		
	Lovenox	Lovenox	Heparin
Indications	40 mg q.d. SC	30 mg q12h SC	15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis[2]		n = 786 31 (4%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis			
Peri-operative Period[3]	n = 288 4 (2%)		
Extended Prophylaxis Period[4]	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis[2]		n = 294 3 (1%)	n = 225 3 (1%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.

[2] Lovenox 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

[3] Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

[4] Lovenox 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox patients versus 1.8% of the placebo patients.

Table 4
Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness[1]

	Dosing Regimen		
	Lovenox[2]	Lovenox[2]	Placebo[2]
Indications	20 mg q.d. SC	40 mg q.d. SC	
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

[2] The rates represent major bleeding on study medication up to 24 hours after last dose.

Table 5
Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment[1]

	Dosing Regimen[2]		
	Lovenox	Lovenox	Heparin
Indication	1.5 mg/kg q.d. SC	1 mg/kg q12h SC	aPTT Adjusted IV Therapy
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

[2] All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox or standard heparin therapy and continuing for up to 90 days.

Table 6
Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

	Dosing Regimen	
	Lovenox[1]	Heparin[1]
Indication	1 mg/kg q12h SC	aPTT Adjusted IV Therapy
Unstable Angina and Non-Q-Wave MI[2,3]	n = 1578 17 (1%)	n = 1529 18 (1%)

[1] The rates represent major bleeding on study medication up to 12 hours after dose.

[2] Aspirin therapy was administered concurrently (100 to 325 mg per day).

[3] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥ 3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Table 7
Major Bleeding Episodes in acute ST-segment Elevation Myocardial Infarction

	Dosing Regimen	
	Lovenox[1]	Heparin[1]
Indication	Initial 30-mg IV bolus followed by 1 mg/kg q12h SC	aPTT Adjusted IV Therapy
acute ST-segment Elevation Myocardial Infarction	n = 10176 n (%)	n = 10151 n (%)
- Major bleeding (including ICH)[2]	211 (2.1)	138 (1.4)
- Intracranial hemorrhages (ICH)	84 (0.8)	66 (0.7)

[1] The rates represent major bleeding (including ICH) up to 30 days

[2] Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by ≥ 5 g/dL. ICH were always considered major.

Thrombocytopenia:

[See *Warnings and Precautions (5.5)*]

Elevations of Serum Aminotransferases

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox should be interpreted with caution.

Local Reactions

Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox.

Other

Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox group, are provided below [see Tables 8 to 11].