



INFECTIOUS DISEASE

Treating acute cystitis effectively the first time, and more clinical guidance on preventing, identifying, and managing infection



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This year I focus on four interesting and clinically relevant studies:

- an article by Huang and colleagues addressing the important issue of how best to reduce the frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in critically ill patients hospitalized in the intensive care unit (ICU)
- a study by Duggal and colleagues assessing the value of perioperative oxygen supplementation to reduce the frequency of postcesarean infection
- an investigation of diagnostic criteria for urinary tract infection (UTI) by Hooton and colleagues
- an exploration of the association between intra-amniotic inflammation, as distinct from bacterial colonization, and adverse fetal outcomes.

For ICU patients, universal decolonization reduces nosocomial infection more than targeted decolonization

Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. 2013;368(24):2255–2265.

Infection in general, and nosocomial infection in particular, is common among patients hospitalized in the ICU. Such patients often are severely immunosuppressed and debilitated. They are likely to have multiple

indwelling catheters and to require mechanical ventilation—interventions that predispose to life-threatening infection. The longer the duration of care in the ICU, the greater the risk of infection, especially infection caused by organisms that have acquired resistance to multiple antibiotics.

In this cluster-randomized trial, Huang and colleagues compared targeted and universal decolonization of patients treated in an

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

The relevance of this investigation for those of us in the field of obstetrics and gynecology is simple and clear: If we have to transfer a patient to an ICU (such as an HIV-infected patient with a serious post-cesarean infection, or an oncology patient with a badly infected surgical wound), she should immediately be started on a regimen of twice-daily nasal mupirocin and daily bathing with chlorhexidine. This straightforward intervention will be of great value in reducing the incidence of bacteremia caused by a particularly dangerous pathogen.

ICU to determine which approach was more effective at preventing nosocomial infection, particularly MRSA infection. They found universal decolonization to be superior to targeted decolonization in reducing these infections.

Details of the study

Investigators conducted their study in 74 ICUs in 43 hospitals. Each hospital

was randomly assigned to one of three interventions:

- Group 1: MRSA screening followed by isolation of colonized patients
- Group 2: MRSA screening followed by isolation and decolonization of MRSA carriers
- Group 3: Universal decolonization (no screening).

The decolonization regimen consisted of twice-daily administration of intranasal mupirocin for 5 days and daily bathing with chlorhexidine-impregnated cloths for the duration of the ICU stay.

The study's two endpoints were 1) the modeled hazard ratios for MRSA clinical isolates and 2) the hazard ratios for bloodstream infection with any pathogen.

During the intervention period, fewer MRSA isolates were found in the universal decolonization group, compared with the other two groups ($P < .01$). In addition, the number of bloodstream infections in the universal decolonization group was significantly lower than in the other two groups ($P < .001$). Fifty-four patients (number needed to treat) needed to undergo decolonization to prevent one bloodstream infection.



Universal decolonization was superior to targeted decolonization in reducing nosocomial infections in the ICU

The jury is still out on supplemental oxygen to reduce surgical site infection

Duggal N, Poddatorri V, Noroozkhani S, Siddik-Ahman RI, Caughey AB. Perioperative oxygen supplementation and surgical site infection after cesarean delivery. *Obstet Gynecol.* 2013;122(1):79–84.

significantly reduced from 11.2% in patients given 30% supplemental oxygen during surgery to 5.2% in those given 80% supplemental oxygen.¹ The oxygen was continued for 2 hours after surgery.

In a later study among general surgery patients, Pryor and colleagues were unable to replicate this finding.² It was in this setting that Duggal and colleagues undertook their investigation among women undergoing cesarean delivery. These investigators, too,

In a widely read study published in 2000 in the *New England Journal of Medicine*, Greif and colleagues demonstrated that, in patients undergoing colorectal surgery, the rate of postoperative wound infection was

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were unable to replicate the 2000 finding of Greif and colleagues.

Details of the study

Over 4 years, from 2006 to 2010, Duggal and colleagues conducted a prospective, randomized, double-blinded controlled trial among patients undergoing scheduled, urgent, or emergent cesarean delivery. All patients were given prophylactic antibiotics, usually cefazolin 2 g intravenously after the infant's umbilical cord was clamped. Surgical technique was reasonably well standardized and included closure of the deep subcutaneous layer of tissue using 2-0 plain gut sutures.

Patients were randomly assigned to receive supplemental oxygen via face mask, at 30% or 80% concentration, during surgery and for 1 hour postoperatively. They were evaluated postoperatively at 2 and 6 weeks. The primary outcome measure was a composite of surgical site infection, endometritis, or both.

A total of 415 women received 30% oxygen and 416 were given 80% oxygen. The two groups were well matched for important confounding variables such as age, race, parity, body mass index, number of prior cesarean deliveries, diabetes, cardiopulmonary disease, anemia, smoking, and chronic steroid use.

The groups did not differ in the frequency of surgical site infection or endometritis, which occurred at a rate of 2.4% in the group receiving 30% oxygen, compared with 2.9% in the group given 80% oxygen.

Rationale for oxygen supplementation

Adequate tissue oxygenation has been observed to enhance the bactericidal function of neutrophils. So why were Duggal and colleagues unable to demonstrate a beneficial effect for oxygen therapy?

The most likely explanations:

- Their obstetric patients were less seriously

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Until additional studies are performed, I cannot recommend routine use of perioperative hyperoxygenation as a method of reducing the rate of surgical site infection and/or endometritis. However, we have very good scientific evidence indicating that the following measures significantly reduce the rate of endometritis after both scheduled and unscheduled cesarean delivery:

- administration of prophylactic antibiotics prior to the start of surgery
- removal of the placenta by gentle traction on the umbilical cord rather than by manual extraction.^{3,4}

Similarly, we have sound evidence demonstrating that the following measures significantly reduce the rate of surgical site infection:

- clipping, rather than shaving, the hair at the surgical site just prior to the incision
- preoperative cleansing of the surgical area with chlorhexidine
- administration of prophylactic antibiotics prior to the start of surgery
- closure of the lower half of the subcutaneous tissue (if it exceeds 2 cm in thickness) using a relatively noninflammatory suture such as polyglactin or polyglycolic acid.

ill than the general surgery patients undergoing colorectal surgery in the study by Greif and colleagues.

- Given the low overall rate of infection, their sample size may have been too small to show a statistically significant difference in outcome (Type II statistical error).

In point of fact, more than 80% of patients in both groups had scheduled cesarean deliveries, presumably prior to the onset of labor and ruptured membranes. The outcome may have been different had the groups included a majority of patients undergoing surgery after labor and ruptured membranes.

FAST TRACK

One technique to reduce the rate of postcesarean endometritis is to remove the placenta by gentle traction on the umbilical cord rather than by manual extraction

The presence of E coli in a midstream urine specimen is highly predictive of UTI

Hooton TM, Roberts PL, Cox ME, Stapleton AE. Voided midstream urine culture and acute cystitis in premenopausal women. *N Engl J Med.* 2013;369(20):1883–1891.

Urinary tract infections (UTI) are among the most common infections experienced by women of all ages. Asymptomatic bacteriuria affects 5% to 10% of all sexually active women. During the course of their lifetime, at least 50% of women develop some form of UTI.

Pyelonephritis is not nearly as common as asymptomatic bacteriuria or cystitis, but this infection can be especially dangerous in older, debilitated women who reside in nursing homes and require indwelling catheters.

The most common organisms that cause UTIs in women are the aerobic gram-negative bacilli, principally *Escherichia coli*, *Klebsiella* species, and *Proteus* species. Other Gram-negative bacilli such as *Pseudomonas* species, *Serratia*, or *Enterobacter* are not common uropathogens except in immunosuppressed hosts or patients who have long-term indwelling catheters. Gram-positive organisms such as group B streptococci, enterococci, and staphylococcal species are occasional pathogens but, as Hooton and colleagues demonstrate in this study, perhaps not quite as important as we once thought.

Details of the study

Using an elegantly simple design, the Hooton team studied women aged 18 to 49 years who had symptoms suggestive of acute cystitis. They collected two urine specimens from each woman for culture—one was collected using the midstream, clean-catch technique and the other by catheterization. They then compared microbial species and colony

counts in the paired specimens to determine the positive and negative predictive values of midstream culture results, using the catheterized culture results as the reference standard.

The 226 women in the study experienced 236 clinical episodes suggestive of acute cystitis. One hundred forty-two (70%) of the catheterized specimens were positive for infection; of these, four specimens yielded more than one uropathogen. One hundred fifty-seven (78%) of the midstream specimens were positive for infection.

The presence of *E coli* in the midstream culture was highly predictive of a positive

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The findings of Hooton and colleagues have several key implications for practicing clinicians:

- When either a pregnant or nonpregnant patient experiences her first episode of acute cystitis, the overwhelming probability is that *E coli* is the infecting pathogen. We can reduce costs by empirically treating the initial infection, thereby avoiding the expense of a urine culture.
- For patients with recurrent infections or for immunocompromised patients, a culture and sensitivity test should be performed because other uropathogens are more likely to be involved and may have less predictable antibiotic susceptibility patterns.
- Contamination of supposed “clean-catch” specimens is very common, and the cultures resulting from these specimens can mislead us in our decisions about antibiotic therapy. Enterococci and group B streptococci are more likely than not to be contaminants from the vaginal flora rather than true infecting pathogens. When they are present in the bladder, they are usually associated with *E coli*. Accordingly, *E coli* should be the principal target of antibiotic therapy.
- To avoid concerns about contamination of specimens in acutely symptomatic patients, obtain the urine specimen by catheter. In the catheterized specimen, the cutoff for true bladder infection should be ≥ 100 colonies/mL. The cutoff of $\geq 100,000$ colonies/mL is applicable only for clean-catch specimens obtained from asymptomatic patients.
- Clinical laboratories should embrace the new cutoff and report even seemingly low colony counts when the urine sample has been obtained by catheterization.



culture for E coli by catheterization, even when the cutoff was only 100 colonies/mL on the midstream specimen (positive predictive value, 93%). However, neither the presence of enterococci nor the presence of group B streptococci, at any colony count, was predictive of a positive culture by catheterization. Interestingly, among 41 patients who had either enterococci or group B streptococci in their midstream culture, E coli was present in the catheterized

culture in 61% of cases, suggesting that infection with E coli may be the more important cause of the patient's symptoms.

Hooton and colleagues concluded that the presence of E coli on a midstream culture, even in low colony counts, is predictive of true bladder infection, as determined by catheterization. However, enterococci and group B streptococci were more likely to be vaginal contaminants or associated with coinfection with E coli, or both.

In preterm labor, amniotic fluid infection without inflammation does not necessarily predict a poor fetal outcome

Combs CA, Gravett M, Garite TJ, et al. Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. *Am J Obstet Gynecol.* 2014;210(2):125.e1–e15.

In this very important clinical investigation, Combs and colleagues collected amniotic fluid from 305 women with preterm labor. They then measured the amniotic fluid concentration of interleukin-6 (IL-6) and assessed for the presence of microbial invasion of the amniotic cavity (MIAC) by either culture or detection of microbial 16S ribosomal DNA. Based on these test results, investigators divided the patients into five groups:

- Infection—defined as positive MIAC and IL-6 >11.3 ng/mL
- Severe inflammation—negative MIAC and IL-6 >11.3 ng/mL
- Mild inflammation—no MIAC and IL-6 from 2.6 to 11.2 ng/mL
- Colonization—positive MIAC and IL-6 <2.6 ng/mL
- Negative—no MIAC and IL-6 <2.6 ng/mL.

The end points of the investigation were latency period and composite perinatal morbidity and mortality. Perinatal morbidity included respiratory distress syndrome, grade 3 or 4 intraventricular hemorrhage, necrotizing enterocolitis, and culture-proven neonatal sepsis.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This study offers several critically important take-home messages:


- Bacterial colonization of the amniotic fluid, without actual inflammation, is not necessarily associated with an ominous outcome for the fetus
- Varying degrees of inflammation exist
- The more intense the inflammation, the worse the outcome for the baby
- The logical clinical application of this investigation is to modify our practice so that, when we perform an amniocentesis for patients with preterm labor, we look not only for bacterial growth but for the presence of key inflammatory mediators in the amniotic fluid, such as IL-6
- A rapidly available, inexpensive, and easy-to-perform assay for IL-6 would be invaluable in improving our ability to assess patients for subclinical infection and inflammation
- An important question, of course, is whether early implementation of specific anti-inflammatory therapy could alter the prognosis for the fetus in selected cases.

Interestingly, the infection and severe inflammation groups had similar short latency periods (median of <1 and 2 days, respectively) and similar rates of composite perinatal morbidity and mortality (81% and 72%, respectively).

The colonization and negative groups also had similar latency periods (median of 23.5 and 25 days, respectively) and similar rates of composite morbidity and mortality

(21% and 25%, respectively).

The mild inflammation group had intermediate outcomes.

When Combs and colleagues used multivariate analysis to adjust for gestational age at enrollment, amniotic fluid IL-6 concentrations greater than 11.3 ng/mL and in the range of 2.6 to 11.3 ng/mL—but not MIAC—were associated with increased composite perinatal morbidity and mortality. 

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