Fertility control

Oral administration of the cyclooxygenase-2 (COX-2) inhibitor meloxicam blocks ovulation in non-human primates when administered to simulate emergency contraception

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Background: Prostaglandins produced via cyclooxygenase-2 (COX-2) within the periovulatory follicle are required for successful ovulation. Inhibition of follicular prostaglandin synthesis prevents timely follicle rupture and oocyte release. This study was conducted to determine if a 5-day course of oral administration of the COX-2 inhibitor meloxicam can prevent ovulation while maintaining normal menstrual cycles in non-human primates.

Methods: Adult female cynomolgus monkeys were studied in each of four sequential menstrual cycles. In Cycle 1, a serum sample was obtained each day and assayed for estradiol, progesterone and luteinizing hormone; first menses was also noted to establish parameters of a normal menstrual cycle for each animal. In Cycle 2, meloxicam was administered orally once each day for 5 days beginning at either mid follicular (n = 4), late follicular (n = 4) or periovulatory (n = 4) phase of the menstrual cycle; daily serum samples and menses were assessed as for Cycle 1. In Cycle 3, the follicle-bearing ovary was removed 2 days after the expected day of ovulation (n = 3–4/treatment group). In Cycle 4, monkeys received the 5-day courses of oral meloxicam as in Cycle 2 (n = 3–4/treatment group), and the remaining ovary was removed. Ovaries were examined for the presence of an oocyte within the follicle.

Results: Monkeys had the expected levels of changing reproductive hormones during Cycle 1. Meloxicam treatment in Cycle 2 did not alter hormone levels or the luteal phase length. Follicles of ovaries removed during Cycle 3 did not contain oocytes, indicating successful ovulation. Follicles did contain oocytes after meloxicam treatment beginning in the mid follicular (67%), late follicular (100%) or periovulatory (50%) phase of Cycle 4, indicating failure of ovulation.

Conclusions: A 5-day course of oral meloxicam administered around the time of ovulation reduced the rate of oocyte release without alteration of reproductive hormones or menstrual cycle length. Meloxicam may be effective as an emergency contraceptive in women.

Key words: prostaglandin / follicle / ovulation / monkey / COX-2 inhibitor

Introduction

Emergency contraception is needed after unprotected intercourse or when failure occurs with the primary contraceptive method. Emergency contraceptives currently available include estrogen plus progesterin combined pills (Yuzpe regimen), progesterin only (levonorgestrel) and progesterone receptor modulators such as mifepristone (Von Hertzen and Godfrey, 2009). These steroidal methods can have side effects, including inappropriate bleeding, which can create difficulties in determining the start of the next cycle. Effectiveness of currently available emergency contraceptive methods varies. For example, in nine studies including a total of 9500 women using levonorgestrel for emergency contraception, a woman’s chance of pregnancy was reduced by 59–94% (Stewart et al., 2007; Chang et al., 2008), thus supporting the need for additional, and ideally non-steroidal, options for emergency contraception.

Inhibition of prostaglandin synthesis may provide a novel target for the development of emergency contraceptives. Prostaglandins produced within the ovulatory follicle are necessary for successful ovulation. Prostaglandins stimulate many periovulatory processes,
including expansion of the cumulus granulosa cells (Eppig, 1981; Hizaki et al., 1999) and enhancement of protease activities which degrade extracellular matrix (Reich et al., 1991; Markosyan and Duffy, 2009). These and other periovulatory processes are essential for successful oocyte release and, therefore, fertility. The rate limiting step in prostaglandin production is catalyzed by the enzyme cyclooxygenase (COX) (Smith, 1997). In periovulatory follicles, the COX-2 isoform is responsible for prostaglandin production. COX-2 expression by granulosa cells increases after the ovulatory luteinizing hormone (LH) surge (Wong and Richards, 1991; Sirois, 1994; Duffy and Stouffer, 2001). Inhibition of COX-2 activity limits follicular prostaglandin production, prevents follicle rupture and blocks oocyte release, supporting a key role for COX-2 in the ovulatory process (Duffy and Stouffer, 2002; Peters et al., 2004).

Because COX-2 activity is required for successful ovulation, drugs which inhibit COX-2 activity may be effective as contraceptives. Reports of infertility in women taking COX inhibitors support the concept that oral COX inhibitors can have contraceptive effects (Akil et al., 1996; Mendonca et al., 2000). Oral administration of COX-2 selective inhibitors to women around the expected time of ovulation prevents or delays follicular collapse (Pall et al., 2001; Bata et al., 2006), which is indicative of a failure of follicle rupture. However, these studies have not confirmed that oral COX inhibitor administration prevents oocyte release.

The COX-2 inhibitor meloxicam (Noble and Balfour, 1996) has excellent potential for development as an emergency contraceptive. This generic drug is inexpensive and is available over the counter in many countries outside the USA. Administration of meloxicam to women for 5 days around the expected time of ovulation delays or prevents follicular collapse (Bata et al., 2006). Recently, Jesam et al. (2009) showed that the COX-2 selective inhibitor meloxicam can delay follicle rupture in 50–91% of women, depending on the dose. In addition, these women maintained normal menstrual cycles as defined by serum estradiol and progesterone levels, so meloxicam may provide an alternative to prevent pregnancy without the side effects of steroidal emergency contraceptives. However, these studies only used vaginal ultrasound to measure the size of the leading follicle as a surrogate marker for lack of rupture and failure of oocyte release. The present study was therefore performed using a non-human primate, the cynomolgus macaque, to determine if administration of meloxicam during the follicular phase of the menstrual cycle blocks oocyte release while permitting maintenance of normal menstrual cycles.

**Materials and Methods**

**Animals**

Adult female cynomolgus macaques were housed at Eastern Virginia Medical School (Norfolk, VA, USA). All animal protocols were approved by the Eastern Virginia Medical School Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health’s Guide for the Care and Use of Laboratory Animals. Animal husbandry and sample collections were performed as described previously (Duffy et al., 2005). Briefly, adult females with regular menstrual cycles were checked daily for menstruation; the first day of menstruation was designated Day 1 of the menstrual cycle. Blood samples were obtained under ketamine chemical restraint (5–10 mg/kg body weight) by femoral or saphenous venipuncture, and serum was stored at −20°C until assayed. Animals were 39–42 months of age at the beginning of the study period; previous history of pregnancy was not available.

**Hormone assays**

Menstrual cycles were monitored by the determination of estradiol and progesterone concentrations in daily serum samples (Chaffin et al., 1999) using the Immulite Clinical Assay Instrument (Siemens Medical Diagnostics Solution; Flanders, NJ, USA), with intra- and inter-assay coefficients of variation less than 10% (Albrecht et al., 2000). Serum LH radioimmunoassay (RIA) was performed by the Endocrine Technology and Support Laboratory, Oregon National Primate Research Center (Dr Francis Pau, Beaverton, OR, USA) using a double-antibody RIA procedure similar to that described by Niswender and Spies (1973). The LH RIA kit and cynomolgus-specific reagents were obtained from Dr Albert Parlow (National Hormone and Peptide Program, Harbor-UCLA Medical Center, Los Angeles). This is a homologous cynomolgus macaque assay with cynomolgus LH (AFP-6936A) for both iodination and standards. The rabbit anti-cynomolgus LH, AFP-342994, was used at a final dilution of 1:972 973. The lower limit of detection was 0.015 ng/tube. The intra-assay variation was 6.6%. All LH determinations were performed in a single assay. Previously, inter-assay variation was determined to be less than 10%.

**Experimental design**

Previous studies indicate that the period during which intercourse can result in pregnancy is comprised of the 4 days leading up to ovulation plus the actual day of ovulation; intercourse after ovulation rarely results in pregnancy (Wilcox et al., 1995). The treatment plan was designed to determine if a 5-day course of oral meloxicam administration could prevent ovulation if treatment was initiated at any time during this fertile period (Fig. 1). Therefore, three treatment groups were utilized (n = 4 animals/group). Animals assigned to the mid follicular group received vehicle or meloxicam for 5 days such that the last day of drug administration was the day of the mid-cycle LH peak. Animals assigned to the late follicular group received vehicle or meloxicam such that the mid-cycle LH peak occurred midway through the 5 days of treatment. Animals assigned to the periovulatory group received vehicle or meloxicam for 5 days such that the first day of drug administration was the day of the mid-cycle LH peak. Retrospective analysis of data confirmed that all treatments were initiated on the anticipated Day ± 1. Previous studies have demonstrated that removal of a single ovary does not alter the timing or hormone levels of subsequent menstrual cycles (Goodman and Hodgen, 1979).

Although the day of the mid-cycle LH peak is typically the day of or the day after the mid-cycle estradiol peak, peak estradiol levels can vary widely between animals (Weick et al., 1973). Therefore, the vehicle treatment cycle with daily blood sampling was performed first to obtain baseline data regarding estradiol levels for each animal; this cycle also confirmed that each animal had a normal menstrual cycle under experimental conditions. The following treatment cycle included meloxicam administration and daily blood sampling. Subsequent treatment cycles (vehicle and meloxicam) were then performed to remove ovaries for histological examination (Fig. 1). Each animal experienced a total of four study cycles, with at least one menstrual cycle between study cycles for rest and recovery.

Meloxicam dose was calculated based on a dose shown previously to be effective in humans (30 mg daily) (Bata et al., 2006; Jesam et al., 2009). Typical body weight for non-obese women in the target age group for contraceptive use (15–40 years old) is 65 kg. Meloxicam (0.5 mg/kg body weight/day) was administered to monkeys orally in food treats. Vehicle consisted of food treats without drug.
**Histology**

Ovaries were obtained at aseptic surgery performed in a dedicated surgical suite under isoflurane anesthesia and involved midline laparotomy. Ovaries were fixed in 4% paraformaldehyde, embedded in paraffin and serial sectioned at 4 μm. Sections were heated to 37°C overnight, heated to 55°C for 30 min, deparaffinized in xylene and rehydrated in a graded series of ethanol and phosphate-buffered saline (PBS). Every other section was stained with hematoxylin to visualize ZP1 immunodetection before counterstaining with acid fuchsin/picric acid solution for 5 min, rinsed with PBS plus 2% horse serum (Vector Labs, Burlingame, CA, USA) for 1 h at room temperature, the primary antibody against human ZP1 (20 μg/ml; Santa Cruz Biotechnology, Santa Cruz, CA, USA) was applied and incubated for 1 h at room temperature, followed by further incubation overnight at 4°C. The anti-goat Vectastain ABC kit with DAB substrate (Vector) was used to visualize ZP1 immunodetection before counterstaining with hematoxylin, dehydration and coverslipping.

Collagen was detected by acid fuchsin staining using a modification of published methods (Luna, 1968). Briefly, sections were incubated in a saturated (14%) acid fuchsin/picric acid solution for 5 min, rinsed with tap water, dehydrated in graded ethanol and xylene and coverslipped.

**Results**

All animals had normal menstrual cycles before, during and after 5 days of vehicle treatment beginning at mid follicular, late follicular or periovulatory phase of the menstrual cycle (Goodman and Hodgen, 1979). Serum estradiol levels increased to peak levels at mid-cycle, generally the day before or the day of peak LH levels (Fig. 2). Serum estradiol levels then dropped to lower levels, typical of the luteal phase. After the mid-cycle LH peak (Day 0), serum progesterone levels showed the typical rise, plateau and fall in advance of menstruation. Luteal phase length, defined as the number of days between the peak serum LH level and the first day of menstruation, was typical for macaques (Table I).

Administration of meloxicam for 5 days beginning at the mid follicular, late follicular or periovulatory phase of the menstrual cycle did not alter serum steroids, peak LH levels or luteal phase length (Fig. 2 and Table I). During meloxicam treatment cycles, all animals had serum levels of estradiol, progesterone and peak LH which were not different from serum hormone levels measured in vehicle treatment cycles. There was no difference in luteal phase length between vehicle and meloxicam treatment cycles. Therefore, oral meloxicam treatment for 5 days did not alter these parameters of normal menstrual cycles.

In subsequent menstrual cycles, daily serum samples were obtained for measurement of estradiol, progesterone and LH to monitor progress of menstrual cycles. Vehicle or meloxicam was administered for 5 days beginning at mid follicular (n = 3), late follicular (n = 4) or periovulatory (n = 4) phase of the menstrual cycle. Ovariectomy to remove the ovary with the dominant structure was performed on luteal Day 4. Removal of the correct ovary after vehicle treatment was confirmed by either menstruation or low serum progesterone within days of surgery. Serial sections of each ovary were examined for the presence of an oocyte trapped within the dominant structure. Each ovary recovered contained a single, large luteinized follicle. Oocytes were not observed in the luteinized follicles of ovaries removed during vehicle treatment cycles (Table II). In contrast, oocytes were observed in 8 of 11 ovaries removed during meloxicam treatment cycles. In ovaries obtained after meloxicam treatment during the mid follicular phase with meloxicam, two of three ovaries had oocytes, which were visible within the antrum of the follicle (Fig. 3A and B). Each of these oocytes was surrounded by a small number of presumably granulosa cells as well as numerous red blood cells. In ovaries from the late follicular and periovulatory meloxicam treatment cycles, oocytes were observed at the perimeter of the
In four of six ovaries, granulosa cells surrounding the oocyte appeared to fail to undergo cumulus expansion (Fig. 3C and D). To confirm that these oocytes were contained within the luteinized follicle, acid fuchsin staining was performed (Fig. 3E). A bright pink stain representing collagen detection was observed surrounding the luteinized follicle; however, collagen staining within the granulosa cells was fainter and similar between compact and luteinized granulosa cells. In the remaining two ovaries from meloxicam treatment cycles, oocytes observed near the perimeter of the follicle were surrounded by granulosa cells which were similar in appearance to the luteinized granulosa cells seen elsewhere in the follicle (Fig. 3F).
stained for the oocyte-secreted zona pellucida protein ZP1 confirmed the identification of oocytes (Fig. 3F, inset).

Previous studies in women indicated that oral COX-2 inhibitor administration may delay follicle rupture (Pall et al., 2001; Bata et al., 2006; Jesam et al., 2009). In the present study, ovariectomy was performed on luteal Day 4, 2 days after the expected day of follicle rupture to allow ample time for oocyte release. Ovulation sites, with continuity between the follicle antrum and the exterior of the ovary, were not consistently observed in any treatment group after vehicle or meloxicam administration. The majority of ovaries from both vehicle and meloxicam treatment cycles had a clearly defined follicle apex which either failed to rupture completely or had healed to cover the rupture site prior to ovary removal (data not shown).

### Discussion

This is the first study to demonstrate that oral administration of a COX-2 inhibitor can prevent oocyte release in primates. Studies performed in the 1970s demonstrated that inhibition of prostaglandin synthesis with indomethacin blocked ovulation in mammals, including primates (Armstrong and Grinwich, 1972; Wallach et al., 1975). It was later shown that indomethacin had a similar effect in women (Killick and Elstein, 1987). The discovery of the COX-2 isoform of COX (Hla and Neilson, 1992) and expression of COX-2 in ovarian granulosa cells just before ovulation (Sirois, 1994; Sirois and Dore, 1997; Duffy and Stouffer, 2001) spurred interest in the ability of prostaglandins produced via COX-2 to regulate periovulatory events (Richards, 1997). Development of inhibitors selective for the COX-2 isoform allowed demonstration that blockade of intraovarian COX-2 activity resulted in failure of follicle rupture and oocyte release (Mikuni et al., 1998; Duffy and Stouffer, 2002; Peters et al., 2004). Studies in women confirmed that oral COX-2 inhibitors administered around the time of the ovulatory LH surge can prevent or delay follicle rupture as assessed by ultrasound (Pall et al., 2001; Bata et al., 2006; Jesam et al., 2009). The present study confirms and extends these results by demonstrating for the first time that oral COX-2 administration resulted in oocytes trapped within luteinized follicles. Taken together, these data support further investigation of COX-2 inhibitors as emergency contraceptives.

An essential periovulatory action of prostaglandins is the stimulation of cumulus expansion. Expansion of cumulus granulosa cells is necessary for detachment of the cumulus–oocyte complex from the follicle wall, which makes the oocyte available in the follicle antrum for release at follicle rupture. In the present study, two oocytes were located in the follicle antrum, so cumulus expansion likely occurred in these follicles. In additional ovaries, oocytes were located near the follicle basement membrane, so the cumulus–oocyte complex did not properly detach from the follicle wall. In a previous study, monkey follicles injected with the general COX inhibitor indomethacin (Duffy and Stouffer, 2002) yielded oocytes surrounded by large, luteinizing granulosa cells near the basement membrane of the follicle. The presence of oocytes near the follicle basement membrane indicates a failure of some aspect of cumulus expansion, even though surrounding granulosa cells appear luteinized in some cases. During the process of cumulus expansion, granulosa cells loosen their cell–cell contacts, secrete a matrix enriched in hyaluronic acid and eventually break free of the follicle wall to form a cumulus–oocyte complex in the follicle antrum, available for release at follicle rupture (Freeman, 1988). Failure of cumulus expansion was identified as one cause of reduced fertility in mice lacking COX-2 expression (Lim et al., 1997; Hizaki et al., 1999). In rodent cumulus cells, prostaglandins stimulate expression of HAS2 and TSG6 (Eppig, 1981; Ochsner et al., 2003), both of which are necessary for successful cumulus expansion. Prostaglandins may also regulate expression of these or other specific genes which contribute to cumulus expansion in primates.

Prostaglandins are also required for normal follicle rupture. Follicle rupture requires thinning and, ultimately, dissolution of matrix components between the follicle antrum and the exterior of the ovary.

### Table I Menstrual cycle parameters during vehicle and meloxicam treatment cycles

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Peak LH levels (ng/ml)</th>
<th>Length of luteal phase (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Meloxicam</td>
</tr>
<tr>
<td>Mid follicular</td>
<td>29.5 ± 6.8</td>
<td>23.2 ± 7.7</td>
</tr>
<tr>
<td>Late follicular</td>
<td>18.0 ± 2.5</td>
<td>11.9 ± 2.0</td>
</tr>
<tr>
<td>Periovulatory</td>
<td>10.4 ± 2.3</td>
<td>16.1 ± 4.3</td>
</tr>
</tbody>
</table>

All data presented as (mean ± SEM), n = 4/group. For each treatment group, no differences were found between vehicle and meloxicam treatment by two-tailed, paired t-test.

### Table II Oocytes in vehicle and meloxicam-treated ovaries

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Oocytes present</th>
<th>Location of oocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Meloxicam</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>Meloxicam</td>
</tr>
<tr>
<td>Mid follicular</td>
<td>0 of 3</td>
<td>2 of 3</td>
</tr>
<tr>
<td>Late follicular</td>
<td>0 of 4</td>
<td>4 of 4</td>
</tr>
<tr>
<td>Periovulatory</td>
<td>0 of 4</td>
<td>2 of 4</td>
</tr>
</tbody>
</table>
Granulosa cells at the follicle apex and the surface epithelium overlaying the rupture site must also be removed. In primates, luteinized tissue typically protrudes through the rupture site to form an ovulatory stigmata. Previous studies in humans have suggested that oral COX-2 inhibitor administration could result in delayed ovulation (Pall et al., 2001; Bata et al., 2006), so in the present study ovaries were removed on luteal Day 4, or 2 days after the expected day of ovulation to permit ample time for follicle rupture to occur. In all control ovaries and in the majority of meloxicam ovaries, follicle rupture could not be confirmed histologically. It is possible that the follicle ruptured and then healed or, alternatively, that rupture did not occur. Previous studies involving injection of the COX inhibitor indomethacin directly into the monkey periovulatory follicle demonstrated that indomethacin either prevented follicle rupture or reduced the size of the ovulatory stigmata.

**Figure 3** Oocytes located within ovaries obtained from meloxicam treatment cycles. (A) Oocyte (arrowhead) within follicle antrum after treatment with meloxicam during the mid follicular phase. (B) Higher magnification of oocyte in (A) shows surrounding (presumably granulosa) cells (arrowhead) and numerous red blood cells. (C–E) Location of an oocyte near the perimeter of a follicle after treatment with meloxicam during the late follicular phase. (C) Oocyte (*) is located near the follicle perimeter (arrow). (D) This germinal vesicle intact oocyte is surrounded by compact granulosa cells. (E) An ovarian section adjacent to the section in (C and D) was stained to detect collagen (bright pink), a major component of the follicle basement membrane. Arrow indicates the perimeter of the follicle; arrowhead shows the lack of similar strong staining between the unexpanded granulosa cells surrounding the oocyte and the luteinized granulosa cells of the follicle. (F) Oocyte surrounded by luteinized granulosa cells within a follicle after treatment with meloxicam during the late follicular phase; inset shows ZP1 immunostaining (brown) of oocyte and surrounding zona pellucida on adjacent tissue section. Tissues in (A–D, F) were stained with hematoxylin and eosin; tissue in (E) was stained with acid fuchsin and hematoxylin. In all images, an, antrum; lgc, luteinized granulosa cells; st, stroma. Bar in (A) should be used for all images. Bar = 100 μm for (A and C); bar = 25 μm for (B, D–F).
rupture site and resulting ovulatory stigmata (Duffy and Stouffer, 2002). Substantial evidence supports a role for prostaglandins in the regulation of ovarian collagenase activity necessary for follicle rupture (Curry and Osteen, 2003). Prostaglandins have been implicated in regulation of the matrix metalloproteinase and plasminogen activator families of proteases in the ovary (Murdoch et al., 1986; Reich et al., 1991; Marksoyan and Duffy, 2009). Indomethacin also decreases apoptotic cell death of both granulosa cells and surface epithelial cells at the follicle apex in sheep, though it is unclear if this action of indomethacin is dependent on prostaglandin synthesis (Murdoch, 1996). Taken together, these studies do indicate that inhibition of ovarian COX-2 activity will effectively prevent follicle rupture.

Serum levels of estradiol and progesterone were not affected by the 5-day meloxicam treatment in the present study. Peak serum LH was also unaffected by meloxicam, suggesting that meloxicam did not prevent the mid-cycle LH surge, although it is important to note that a single daily blood sample is suboptimal for accurate measurement of peak LH levels. Monkeys experienced timely menstruation, consistent with the unchanged hormonal milieu. Similar results were obtained when women received COX-2 inhibitors around the time of ovulation for up to 9 days (Pall et al., 2001; Bata et al., 2006). Because ovarian steroidogenesis was unchanged during and after meloxicam treatment, locally produced prostaglandins do not appear to regulate follicular steroidogenesis. Steroid hormone levels were unchanged after meloxicam treatment, suggesting that formation of the corpus luteum proceeded normally. These findings are consistent with reports in cow (Peters et al., 2004) and monkey (Duffy and Stouffer, 2002) where COX inhibitor administration around the time of ovulation yielded normal estrogen and progesterone levels throughout the remainder of the reproductive cycle. These findings contrast with studies in rodents, which suggest that prostaglandin E2 produced within the follicle regulates progesterone synthesis (Elvin et al., 1999). Species differences may result from the differences in the stimulus for the formation of the corpus luteum in rodents when compared with bovine and primates, which have long-lived corpora lutea (Rothchild, 1981).

Side effects, including negative cardiovascular events, led to the withdrawal of some COX-2 inhibitors from the market and reduced interest in daily COX-2 inhibitor administration. While a low risk of serious side effects has been associated with COX-2 inhibitor administration in older people (Layton et al., 2003a, b; Helin-Salmivaara et al., 2006), young adult women are the target population for contraceptive use. A short course of administration of the COX-2 inhibitor meloxicam as an emergency contraceptive would have low potential for the side effects. In the previous studies in humans, once daily administration of meloxicam yielded reports of limited side effects (Pall et al., 2001; Bata et al., 2006; Jesam et al., 2009). In general, serious side effects were rarely observed in prospective studies of young adults receiving various COX-2 inhibitors daily for up to 14 days (Graff et al., 2007) or in retrospective studies of young adults who were prescribed COX-2 inhibitors for a minimum of several months (Layton et al., 2003a,b; Helin-Salmivaara et al., 2006). Once daily meloxicam administration from Days 5–21 of the menstrual cycle might therefore be an effective contraceptive. However, additional studies will be needed to determine whether this regimen of COX-2 inhibitor administration will be well tolerated by women.

Authors’ Roles

K.E.H.: acquisition and analysis of data, drafting of the manuscript, final approval of the version to be published. M.J.K.H.: conception and design, revision of the manuscript, final approval of the version to be published. D.M.D.: conception and design, acquisition, analysis, and interpretation of data, drafting and critical revision of the manuscript, final approval of the version to be published.

Funding

Support for this project [CIG-07-115] was provided by CICCR, a program of CONRAD, Eastern Virginia Medical School. The views expressed by the authors do not necessarily reflect the views of CONRAD or CICCR.

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Submitted on July 27, 2009; resubmitted on October 30, 2009; accepted on November 5, 2009.