Outbreak of *Serratia marcescens* Infections following Injection of Betamethasone Compounded at a Community Pharmacy

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(See the editorial commentary by Pegues on pages 838–40)

**Background.** In June 2001, following the report of 4 patients with *Serratia marcescens* meningitis who received epidural injections of betamethasone compounded at a community pharmacy, we initiated an outbreak investigation.

**Methods.** All patients who received injections of betamethasone from the production lot common to the 4 patients were evaluated. A case patient was defined as a patient who received compounded betamethasone and had *S. marcescens* isolated from a sterile site or clinical and laboratory evidence of infection. We cultured all recovered betamethasone, environmental specimens from the pharmacy, and medications recovered from an ambulatory surgery center. The California Board of Pharmacy reviewed the procedures used to prepare the betamethasone.

**Results.** We identified 11 patients with culture-confirmed *S. marcescens* (8 patients) or clinical infection (3 patients) following injection of compounded betamethasone from 25 May through 31 May 2001. Case patients had meningitis (5 patients, with 3 deaths), epidural abscesses (5 patients), or an infected hip (1 patient). *S. marcescens* was isolated from 35 (69%) of 51 betamethasone vials recovered, from pharmacy specimens of 1% carboxymethylcellulose stock solution, from pharmacy surfaces, and from multiple parenteral materials used at the ambulatory surgery center. Pulsed-field gel electrophoresis patterns of *S. marcescens* isolates of representative specimens from patients, the betamethasone, the pharmacy, and the ambulatory surgery center were identical. Deficient practices in compounding of betamethasone included inadequate autoclaving temperatures and failure to perform terminal sterilization.

**Conclusions.** This outbreak of serious *S. marcescens* infection followed improper compounding of betamethasone in a community pharmacy. Enforceable national standards for pharmaceutical compounding are needed to reduce the risk of such outbreaks.
METHODS

Case finding, study definitions, and study period. All physicians who received any compounded injectable product from pharmacy X within the previous 6 months were notified and requested to examine their patients for infectious complications. Local hospital infection-control practitioners were asked to report culture-positive S. marcescens CNS and joint infections that had occurred in the previous 6 months. An outbreak case patient was defined as any individual who had received compounded injectable betamethasone with evidence of clinical infection (i.e., anyone who had a culture-positive specimen obtained from a normally sterile site or a culture-negative infection with supporting laboratory and clinical evidence of infection). The study period was from 1 February 2001, when pharmacy X began compounding injectable betamethasone, through 4 June 2001, when the last administration of compounded betamethasone occurred.

Patient study. All patients who received epidural and intra-articular betamethasone at ASC A from 22 May through 31 May 2001 were notified and evaluated by an infectious disease physician. The evaluation included medical history, physical examination, 2 blood culture sets, urine culture, WBC count with differential, platelet count, determination of erythrocyte sedimentation rate, determination of C-reactive protein level, and radiographic studies as indicated (MRI of spine or joint). Individuals who showed no evidence of infection received a prophylactic antimicrobial regimen of ceftriaxone (a 2-g dose administered intravenously daily for 1 week) and were examined weekly for 12 weeks. The epidural and intra-articular injection procedures, performed by 1 physician at ASC A, were observed by the investigation team. All patients who received ophthalmologic betamethasone during a cataract procedure at ASC A and patients who received intra-articular betamethasone at the orthopedic offices were examined by their respective physicians for ocular and joint infections.

Pharmacy study. We reviewed records at pharmacy X to determine when the betamethasone administered to the patients with S. marcescens meningitis had been compounded. The pharmacy distribution records were reviewed to identify other patients exposed to compounded betamethasone from the production lot associated with the meningitis cases. All injectable pharmaceutical products compounded by pharmacy X in the 6 months before the compounding of the betamethasone production lot that was implicated in the meningitis cases were recalled by the Contra Costa County Public Health Department. Physicians and health care facilities that received injectable products were requested to immediately cease their use and to transport all available vials to the Contra Costa County Public Health Laboratory. The California Board of Pharmacy conducted an independent concurrent investigation of compounding with respect to betamethasone preparation, record keeping, and training practices at pharmacy X.

Microbiologic studies. All recalled betamethasone was cultured. At ASC A, all items associated with the epidural and joint injection procedures (lidocaine, sodium bicarbonate, sodium chloride, alcohol solution, and iohexol) and betamethasone were recovered from a sharps container and cultured. Selected items used in other procedures and sealed vials of these products from the same lots of manufacture were also obtained and cultured. Environmental surfaces at pharmacy X, including the sink, hood counter, hood bar, balance, homogenizer, sink drain board, sink area, and sink faucet, were swabbed and cultured. Samples of tap water, individual component ingredients (both dry and in solution) of betamethasone stock solution, and the remaining amount (7 mL) of a 100-mL vial of betamethasone stock solution compounded on 9 May 2001 were also cultured. All cultures were performed at the Contra Costa County Public Health Laboratory.

Antimicrobial susceptibility testing was performed for all patient S. marcescens isolates at the microbiology laboratory of hospital A using standard Kirby-Bauer techniques. PFGE was performed for all human clinical and selected environmental S. marcescens isolates at the Microbial Diseases Laboratory of the California Department of Health Services (Richmond, CA) after digestion with the Bln 1, Spe 1, Sfi 1, Not 1, and XPA enzymes using standard methods [4] and interpreted according to the criteria of Tenover et al. [5].

RESULTS

Patient study. The initial 4 patients with S. marcescens meningitis received epidural betamethasone with a label preparation date of 17 May 2001. Compounding records at pharmacy X traced the betamethasone to an actual preparation day of 11 May 2001, when 60 5-mL vials were produced. The 60 vials were traced forward to 2 ASCs (ASC A and ASC B) and 2 outpatient orthopedic practices (orthopedic practices A and B) (table 1). All 78 patients who received betamethasone were evaluated for infectious complications. All 18 patients who received conjunctival injections of betamethasone had been administered ophthalmologic gentamicin (to which the S. marcescens was highly susceptible) after their procedures, and none had any evident infection on follow-up. None of the 38 patients who had received intra-articular betamethasone injections from orthopedic practices A and B had any evidence of infection.

At ASC A, 11 of the 22 individuals who had received betamethasone injections for chronic back or joint pain met the definition of an outbreak case patient; 8 (73%) had cultures positive for S. marcescens (table 2). All outbreak case patients had received epidural or intra-articular betamethasone for chronic pain; these patients included 5 with meningitis (4 with positive CSF culture results) and 5 with epidural abscesses (3
Table 1. Distribution of betamethasone vials, patient exposures, and clinical outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ambulatory surgery center A</th>
<th>Ambulatory surgery center B</th>
<th>Orthopedic practice A</th>
<th>Orthopedic practice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of betamethasone vials received</td>
<td>25</td>
<td>10</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Date vials received</td>
<td>17 May 2001</td>
<td>18 May 2001</td>
<td>15 May 2001</td>
<td>11 May 2001</td>
</tr>
<tr>
<td>No. of vials recovered (no. with positive <em>Serratia marcescens</em> culture results)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>24</td>
<td>10</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Unused</td>
<td>1 (1)</td>
<td>10 (10)</td>
<td>4 (1)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Used</td>
<td>23 (23)</td>
<td>0</td>
<td>4 (0)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Patient exposures (no. of patients)</td>
<td>Hip (1), epidural (21),</td>
<td>None</td>
<td>Intra-articular (18)</td>
<td>Intra-articular (20)</td>
</tr>
<tr>
<td>Clinical outcomes (no. of patients), by exposure type</td>
<td>epidural abscess (5), no illness (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>Septic arthritis (1)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Epidural</td>
<td>Meningitis (5), epidural</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>No illness (18)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Intra-articular</td>
<td>...</td>
<td>No illness (18)</td>
<td>No illness (20)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Sixty 5-mL vials were produced and distributed from 11 May to 18 May 2001.

with positive culture results) after epidural injections and 1 patient with a culture-positive hip infection after an intra-articular hip injection. Three patients with meningitis died. Five patients had progressive back pain without fever and MRI findings that were diagnostic of epidural abscess 8–20 days after administration of lumbar epidural betamethasone. MRI showed resolution in all patients after completion of antimicrobial therapy.

Thirty individuals had epidural or joint betamethasone injections at ASC A without evidence of overt infection on initial evaluation. Three of these patients developed epidural abscesses after completing 5–7 days of prophylaxis. The time between betamethasone exposure and the start of prophylaxis for the 3 case patients (mean duration, 8 days; range, 7–9 days) was shorter than that for the 27 individuals who remained free of infection (mean duration, 9.75 days; range, 7–22 days). The 27 patients who remained free of infection had no evidence of secondary infection after 12 weeks of follow-up.

Active case finding did not reveal any *Serratia* infections among patients receiving betamethasone compounded before 11 May 2001, including 16 patients at ASC A who received epidural injections on 22 May, or infection associated with any other products from pharmacy X.

A single physician at ASC A performed all epidural procedures under aseptic conditions. The betamethasone epidural injection involved multiple steps using 4 separate needles and syringes. The first syringe was used for the preparation of betamethasone, a second syringe was used to check for resistance within the spinal canal, a third syringe was used for anesthetic administration, and the fourth syringe was used for contrast to verify spinal needle location. For the betamethasone preparation, a single syringe was used to draw-up a mix of betamethasone, normal saline, and lidocaine, with needles being changed for each component. One vial of iohexol contrast was used for up to 8 different patients. Each of the lidocaine, normal saline, sodium bicarbonate, and betamethasone vials were used for a single epidural or joint injection; however, vials with residual betamethasone were saved for ophthalmologic administration. The betamethasone, iohexol, and normal saline were stored at room temperature.

**Pharmacy study.** Pharmacy X provided injectable betamethasone to ASC A beginning 1 February 2001, when the sole commercial supplier of injectable betamethasone had stopped production [6]. Lots of betamethasone produced before 11 May 2001 were identified and traced. Of 4 lots totaling 95 5-mL vials, 11 vials from 3 lots were recovered from ASC A.

Pharmacy X technicians and pharmacists reportedly followed American Society of Health-System Pharmacists guidelines on quality assurance for pharmacy-prepared sterile products [7], which recommended autoclaving both stock solutions and final products. The California Board of Pharmacy [8] determined that on 11 May 2001 a pharmacy technician autoclaved three 100-mL stock solutions but not the individual vials of betamethasone, as had previously been the practice. The technician reported changing the automated autoclave setting and eliminating terminal sterilization, because autoclaving of previous lots of betamethasone resulted in discoloration of the final product. The 5-mL vials were cleaned with alcohol pads before pipetting the betamethasone product. Overall, the following areas were identified by the California Board of Pharmacy as...
Table 2. Demographic and clinical characteristics of patients with *Serratia marcescens* infection following injection of betamethasone compounded at a community pharmacy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Medical history</th>
<th>Date of injection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time from injection to symptom onset</th>
<th>Clinical diagnosis</th>
<th>Laboratory diagnosis (diagnostic method)</th>
<th>Source of <em>S. marcescens</em></th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>Chronic low back pain, multiple back surgeries</td>
<td>29 May</td>
<td>6 h</td>
<td>Subarachnoid hemorrhage</td>
<td>Subarachnoid hemorrhage (CT scan)</td>
<td>Blood, CSF, urine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ab</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>F</td>
<td>Chronic back pain, unable to walk</td>
<td>29 May</td>
<td>1 day</td>
<td>Meningitis</td>
<td>Meningitis (CSF culture)</td>
<td>CSF, blood</td>
<td>Ab</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>M</td>
<td>Chronic back pain, Parkinson disease</td>
<td>29 May</td>
<td>1 day</td>
<td>Subarachnoid hemorrhage</td>
<td>Subarachnoid hemorrhage (CT scan)</td>
<td>CSF, blood&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ab</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>M</td>
<td>Chronic low back pain, multiple back surgeries</td>
<td>29 May</td>
<td>12 h</td>
<td>Meningitis</td>
<td>Meningitis (CSF culture)</td>
<td>CSF</td>
<td>Ab</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>M</td>
<td>Chronic low back pain, diabetes</td>
<td>31 May</td>
<td>8 days</td>
<td>Meningitis</td>
<td>Meningitis (CSF culture)</td>
<td>Neg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Ab</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>M</td>
<td>Chronic low back pain, spinal stenosis</td>
<td>29 May</td>
<td>1 day</td>
<td>Epidural abscess</td>
<td>Epidural abscess (MRI)</td>
<td>Blood, epidural, Ab, SD</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>87</td>
<td>M</td>
<td>Chronic back pain, bilateral hip replacement</td>
<td>29 May</td>
<td>1 day</td>
<td>Epidural abscess</td>
<td>Epidural abscess (MRI)</td>
<td>Neg&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Ab</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>M</td>
<td>Chronic low back pain</td>
<td>29 May</td>
<td>8 days</td>
<td>Epidural abscess</td>
<td>...</td>
<td>Surgical drainage</td>
<td>Ab, SD</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>M</td>
<td>Chronic low back pain</td>
<td>29 May</td>
<td>15 days</td>
<td>Epidural abscess</td>
<td>Epidural abscess (MRI)</td>
<td>Neg&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Ab</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>M</td>
<td>Chronic low back pain</td>
<td>31 May</td>
<td>13 days</td>
<td>Discitis, epidural abscess</td>
<td>Discitis (MRI)</td>
<td>Epidural</td>
<td>Ab, SD</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>F</td>
<td>Chronic hip pain</td>
<td>24 May</td>
<td>1 day</td>
<td>Hip septic arthritis</td>
<td>...</td>
<td>Synovial fluid</td>
<td>Ab, SD</td>
<td>Survived</td>
</tr>
</tbody>
</table>

**NOTE.** Ab, antibiotic therapy; Neg, culture results negative for *S. marcescens*; SD, surgical drainage.

<sup>a</sup> All dates are 2001.

<sup>b</sup> Cultures obtained for transplant protocol.

<sup>c</sup> Cultures obtained at autopsy.

<sup>d</sup> Gram stain results revealed many WBCs and no organisms; the patient had received antibiotic therapy before samples were obtained for culture.

<sup>e</sup> Blood and urine culture only.
being inadequate with respect to the compounding of betamethasone: sterilization techniques (i.e., inadequate autoclaving temperatures and lack of final autoclaving step), technical staff training, labeling practices, and supervision of pharmacy technicians. Specific deficiencies with regard to other compounded products were not observed.

**Microbiologic studies.** Twenty-four vials of betamethasone recovered from ASC A and all 10 unopened vials recovered from ASC B were culture-positive for *S. marcescens* (table 1). Of the 17 vials recovered from orthopedic offices, 1 unopened vial was culture-positive for *S. marcescens*, and the remaining 16 vials were showed no growth. All vials recovered from lots of betamethasone compounded before 11 May 2001 showed no growth.

At pharmacy X, of the 10 individual ingredients used to compound the betamethasone, only sodium carboxymethylcellulose 1% stock solution (labeled 26 April 2001) grew *S. marcescens*. The methycellulose pellets (not a sterile product) used to make the 1% carboxymethylcellulose solution were no longer present at pharmacy X. *S. marcescens* was isolated from the remaining betamethasone stock solution prepared on 11 May 2001. Cultures from sink handles and the homogenizer interior also yielded *S. marcescens*, whereas other cultures of betamethasone powder stock, betamethasone acetate stock, sterile water, tap water, other stocks and containers, and other compounding work areas had negative results.

At ASC A, a total of 107 discarded products were identified in the sharps container in the surgical suite where epidural and joint procedures were performed from 22 May through 31 May 2001. Cultures were obtained from all 52 items associated with epidural procedures; *S. marcescens* was isolated from 33 (65%) of the items. These included 6 (35%) of 17 vials of iohexol contrast dye (Omnipaque; Nycomed), 11 (85%) of 13 vials of lidocaine, and 16 (80%) of the 20 sodium chloride vials (data not shown). For each of the items previously noted, 2–4 unopened sealed vials from the same lot were cultured, but none revealed bacteriologic growth. Fifty-five additional items not associated with the injection procedure were recovered from the same sharps container; none of the 33 items cultured revealed *S. marcescens*.

*S. marcescens* isolates from the 8 patients with positive culture results had identical antimicrobial susceptibility patterns and biotypes. PFGE patterns were identical for *S. marcescens* isolates from a single patient specimen, betamethasone stock solution, a sealed vial of unused betamethasone, the sink handles and interior of the homogenizer used for compounding betamethasone at pharmacy X, and the lidocaine, sodium bicarbonate, and iohexol vial found in the sharps container at ASC A. PFGE was completed for 8 human clinical isolates using 4 different enzymes; they produced fragments too numerous for accurate PFGE interpretation for 7 of the 8 human isolates.

**DISCUSSION**

This investigation showed that betamethasone compounded on a single day at a community pharmacy was associated with 11 cases of meningitis, epidural abscesses, and septic arthritis that occurred after epidural or joint injections at a single ASC. Characteristics of the *S. marcescens* isolates from patients, opened and unopened betamethasone vials, 1 stock solution, and equipment used by the pharmacy to prepare the betamethasone were consistent with a single source. Because the methycellulose pellets used to prepare the stock solution were not available, the step at which contamination occurred could not be ascertained. That *S. marcescens* was cultured from all 34 vials available from 2 outpatient surgical centers but was only cultured from 1 of 17 vials available from 2 outpatient orthopedic offices suggests that only part of the lot produced on 11 May was contaminated. The pharmacy records were insufficient to determine whether portions of the lot were prepared at different times or using different techniques.

The findings of *S. marcescens* from multiple products used at ASC A documented widespread cross-contamination from the compounded betamethasone or environment to other medications. Whether this cross-contamination contributed to some of the infections could not be determined. Items cross-contaminated during a procedure but used only for that procedure and then discarded would not have contributed to additional infections. The physician performing the procedures used single-use products (with the exception of iohexidol dye) and separate needles for each step in the procedures. Cross-contamination could have occurred if a needle used to draw betamethasone was subsequently used to draw other products (which was not observed during the investigation) or through the contamination of surfaces of additional items with betamethasone and subsequent inoculation into the vial [9]. However, items such as radiologic dyes stored in multi-use containers might have contributed to infections, particularly if sufficient time elapsed between the initial contamination and subsequent uses to allow for amplification [9, 10]. Although we detected no infections in patients who did not receive betamethasone, in view of the frequency of contamination of multi-use vials, the use of such vials should be avoided, particularly if they do not contain preservative agents [10].

Of the 22 patients at ASC A who received epidural or intraarticular injections of contaminated betamethasone, 11 received prophylactic ceftriaxone and did not show any signs of infection. Whether this prophylactic regimen prevented infection in these patients cannot be determined. There is no standard recommendation for antimicrobial prophylaxis for the events described in this outbreak. At the time of this investigation, the extent of the CNS infections was unknown. The prophylactic antimicrobial doses and duration were determined by an experienced infectious disease clinician who recognized the need.

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for adequate CSF penetration. Ophthalmologic administration of contaminated betamethasone to 18 patients at ASC A during cataract removal was not associated with infection, perhaps because of the small quantities used, the defense mechanisms present at this site, and the routine administration of gentamicin prophylaxis. Since this investigation, the use of commercially prepared steroids during cataract procedures continues at ASC A.

Thirty-eight patients were exposed to the compounded betamethasone at 2 orthopedic offices but did not show evidence of infection; however, of the 25 vials distributed to these offices, 17 were cultured, and only 1 unused vial had positive culture results. In addition, the lower quantity of betamethasone and different anatomical locations (knees, elbows, and fingers) at which betamethasone was injected at these offices may have provided a lower risk of infection for these patients, compared with patients treated at ASC A (who received epidural and hip injections). Betamethasone used at ASC A that was compounded at pharmacy X before 11 May 2001 was not associated with any cases of infection, and no other medications compounded at pharmacy X were associated with cases of infection.

To our knowledge, this is the first outbreak of infection associated with pharmaceutical compounding. In 2002, methylprednisolone acetate (compounded at a pharmacy in North Carolina because of a drug shortage) that was supplied to hospitals and pain management clinics in 5 states was responsible for *Exophiala dermatitidis* infections [11]. In our outbreak, the betamethasone was compounded locally to fill the void created by a national shortage of commercially produced betamethasone [12]. As a result of their investigation, the California Board of Pharmacy suspended the licenses of both pharmacists and the pharmacy technician responsible for compounding.

The practice of drug compounding has been reported to be increasing, with an estimated 43,000 compounded medications prepared daily in the United States [11]. The US Food and Drug Administration (FDA) regulates pharmaceutical manufacturing, for the most part ceding the regulation of compounding to state boards of pharmacy. In May 2002, the FDA issued a guidance document on pharmacy compounding, proposing that the FDA consider enforcement action for pharmacies that engage in “compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions” [13, p. 3]. Pharmacy X compounded 300 mL of betamethasone for which there was no evidence of anticipation of or eventual receipt of prescriptions.

Moreover, the use of nonsterile components and equipment compromises the safety of compounding sterile products and could therefore be subject to FDA regulation [14]. The US Pharmacopeia standards for the preparation of sterile products are enforceable by the FDA; a new standard—*Pharmaceutical Compounding: Sterile Preparations*—was adopted on 1 January 2004 [15]. High-risk compounded sterile products should undergo end-product sterility testing before they are dispensed from the pharmacy. Following this outbreak, California Senate Bill 293 was enacted, requiring the California Board of Pharmacy to (1) adopt regulations establishing standards for compounding injectable preparations, (2) require pharmacies that prepare sterile formulations to obtain a special license, and (3) increase investigations of compounding pharmacies. Regulations based on the US Pharmacopeia and American Society of Health-System Pharmacists standards went into effect on 29 October 2004 [16].

This outbreak was the result of improper drug compounding to make up for shortages of a drug formulation. Such drug shortages are an increasing problem [17] and, therefore, increase the potential demand for drug compounding by local or hospital pharmacies. Clinicians will need to stay vigilant for potential infections among patients who have received injections with compounded medications, and health care facilities and medical practices should adhere to strict infection-control practices.

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**References**