Vancomycin Use in Hospitalized Pediatric Patients

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ABSTRACT. Objectives. To assess vancomycin utilization at children’s hospitals, to determine risk factors for vancomycin use and length of therapy, and to facilitate adapting recommendations to optimize vancomycin prescribing practices in pediatric patients.

Methods. Two surveys were conducted at Pediatric Prevention Network hospitals. The first (Survey I) evaluated vancomycin control programs. The second (Survey II) prospectively reviewed individual patient records. Each hospital was asked to complete questionnaires on 25 consecutive patients or all patients for whom vancomycin was prescribed during a 1-month period.

Results. In Survey I, 55 of 65 (85%) hospitals reported their vancomycin control policies. Three quarters had specific policies in place to restrict vancomycin use. One half had at least 3 vancomycin restriction measures. In Survey II, personnel at 22 hospitals reviewed 416 vancomycin courses, with 2 to 25 (median = 12) patients tracked per hospital. Eighty-two percent of the vancomycin prescribed was for treatment of neonatal sepsis, fever/neutropenia, fever of unknown origin, positive blood culture, pneumonia, or meningitis. In an additional 6% (26/416), vancomycin was prescribed for patients with β-lactam allergies and in 13% (56/416) for prophylaxis. Median duration of prophylaxis was 2 days (range: 1–15 days). Almost half (196, 47%) of the patients who received vancomycin were in intensive care units; 27% of the vancomycin courses were initiated by neonatologists and 19% by hematologists/oncologists. The predominant risk factor at the time of vancomycin initiation was the presence of vascular catheters (322, 77%); other host factors included cancer chemotherapy (55, 13%), transplant (30, 7%), shock (24, 6%), other immunosuppressant therapy (17, 4%), or hypoplastic state (2, <1%). Other clinical considerations were severity of illness (96, 23%), uncertainty about diagnosis (51, 12%), patient not responding to current antibiotic therapy (40, 10%), or implant infection (13, 3%). When vancomycin was initiated, blood cultures were positive in 85 patients (20%); cultures from other sites were positive in 45 (11%), and Gram stains of body fluids were positive in 37 (9%). In 29 (7%) patients, organisms sensitive only to vancomycin were isolated before vancomycin initiation. Reasons for discontinuing vancomycin included: therapeutic course completed (125, 30%), negative cultures (106, 25%), alternative antibiotics initiated (75, 18%), illness resolved (14, 3%), or patient expired (13, 3%). Final results of blood culture isolates resistant to β-lactam antibiotics included 48 coagulase-negative staphylococcus, 5 Staphylococcus aureus, and 10 other species.

Conclusions. At children’s hospitals, vancomycin is initiated for therapy in patients who have vascular catheters and compromised host factors. Only 7% had laboratory-confirmed β-lactam-resistant organisms isolated at the time vancomycin was prescribed. Efforts to modify empiric vancomycin use in children’s hospitals should be targeted at intensivists, neonatologists, and hematologists. Initiatives to decrease length of therapy by decreasing the number of surgical prophylaxis doses and days of therapy before laboratory results may decrease vancomycin exposure. Pediatrics 2003;112:e104–e111. URL: http://www.pediatrics.org/cgi/content/full/112/2/e104; vancomycin, pediatrics, antimicrobial resistance, antimicrobial use.

ABBRREVATIONS. MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant enterococci; HICPAC, Hospital Infection Control Practices Advisory Committee; CDC, Centers for Disease Control and Prevention; PPN, Pediatric Prevention Network; NACHRI, National Association of Children’s Hospitals and Related Institutions; MMP, Medical Management Planning; NICU, neonatal intensive care unit; CONS, coagulase-negative staphylococcal species.

Clinical use of vancomycin, a glycopeptide antibiotic licensed in 1956, increased in 1958 with the emergence of penicillinase-producing staphylococci. Following the introduction of methicillin in 1960, vancomycin was rarely prescribed until methicillin-resistant Staphylococcus aureus (MRSA) became prevalent in the 1980s. Vancomycin use continued to increase in the 1980s with the emergence of ampicillin-resistant enterococci and methicillin-resistant coagulase-negative staphylococci, and in the 1990s with the emergence of penicillin-resistant pneumococci. Vancomycin-resistant enterococci (VRE) were first isolated in Europe in 1986 and in the United States in 1988. Prior vancomycin therapy is an independent risk factor for the acquisition of VRE. Recently, vancomycin resistance also has emerged among staphylococcal species. In 1996, a vancomycin-intermediately-sensitive Staphylococcus aureus was reported from Japan. Subsequently, the first United States isolates of vancomycin-intermediately-sensitive S aureus occurred in Michigan and New Jersey in 1997. Streptococcus pneumoniae also have become increasingly resistant.
to penicillins and cephalosporins. In June 2002, the first documented case of infection in the United States caused by vancomycin-resistant S. aureus occurred in a chronic renal failure patient from Michigan. Molecular testing detected the presence of the vanA gene in the patient’s isolate. Vancomycin-resistant Enterococcus faecalis (VRE) was also recovered from a foot ulcer, suggesting transmission of the vanA gene from the enterococcus to the S. aureus. It has been estimated that vancomycin use in the United States increased from 1900 kg/year in 1984 to 10,312 kg/year in 1996.

Widespread use of intravascular and prosthetic devices and increasing antibiotic resistance has resulted in a dramatic rise in vancomycin administration. At one university medical center, a 20-fold increase in vancomycin use during 1981-1991 was reported. Hematology, oncology, and hematopoietic stem cell transplantation patients received more vancomycin than patients on other services. There are limited studies of vancomycin use in the pediatric population. A retrospective chart review conducted at Children’s Health care of Atlanta at Emory described the epidemiology of vancomycin use during 1993–1995. Distribution of vancomycin use by service was: hematology/oncology 28%; neurosurgery 18%; cardiothoracic surgery 13%; neonatology 10%; and general pediatrics 7%. Medicine service patients had a greater proportion of doses (61%) than surgery patients (39%), although surgery service patients were significantly more likely to receive vancomycin than were medicine service patients.

In an attempt to encourage judicious use of vancomycin, the Hospital Infection Control Practices Advisory Committee (HICPAC) of the Centers for Disease Control and Prevention (CDC) published recommendations for appropriate use of vancomycin in 1995. Recommendations did not specifically address pediatric patients or empiric use of vancomycin before laboratory confirmation of resistant organisms. In 1997, the American Academy of Pediatrics recommended empiric use of vancomycin for treatment of definite or probable bacterial meningitis in children older than 1 month. The CDC, the National Foundation for Infectious Diseases, the Society for Healthcare Epidemiology of America, and the Infectious Disease Society of America have individually or jointly published consensus statements urging physicians to reduce inappropriate antibiotic use. Data on acceptance and implementation of the guidelines are limited. A vancomycin use report from a 225-bed tertiary care pediatric teaching hospital during a 6-month period (September 1995 to March 1996) identified 118 patient courses of vancomycin administered. Appropriate vancomycin usage was based on the CDC HICPAC criteria but were modified to accept empiric use for presumed central line infection, presumed pneumococcal meningitis, or pneumococcal infections in critically ill patients, and initial treatment of selected febrile patients with sickle cell anemia. Vancomycin use was inappropriate in 64 (54%) of 118 patients. Reductions in inappropriate use (64% in the first 2 months of the study to 50% in the last 4 months of the study) occurred following a letter sent to physicians describing the modified CDC guidelines.

Three additional studies of vancomycin use have been reported from Children’s Health care at Atlanta and Egleston. In a random sample of 37 patients admitted to the hematology/oncology service, all courses of vancomycin were administered before culture results were available. Eight patients ultimately had cultures positive for Gram-positive bacteria. All isolates were sensitive to antibiotics other than vancomycin. A random sample of 21 patients admitted to the Cardiothoracic Surgery Service who received vancomycin were reviewed. Vancomycin was used as surgical prophylaxis in 6 courses (1 patient had a β-lactam allergy), empiric therapy in 17 courses, and directed therapy based on cultures in 4 courses (2 patients with MRSA, 2 patients with methicillin-resistant Staphylococcus species). A cross-sectional survey on pediatric neurosurgery patients during 1996 identified 30 patients who received 115 doses of vancomycin. Vancomycin was used as empiric therapy in 3 (10%) patients and for prophylaxis in 28 (93%).

The Pediatric Prevention Network (PPN) is a collaborative effort of the CDC and the National Association of Children’s Hospitals and Related Institutions (NACHRI) to conduct multicenter studies of nosocomial infections, antimicrobial use, and antimicrobial resistance in pediatric hospitals. Principal investigators from participating hospitals develop protocols, which then are reviewed by the Steering Committee; PPN hospital personnel participate in projects based on local resources and interest. Vancomycin use was identified by the Steering Committee as an important topic for study.

Medical Management Planning (MMP), Inc, a management consulting firm that works with hospitals to implement productivity and quality solutions, joined forces with the PPN to perform Survey II of the vancomycin project. Since 1992, MMP’s BENCH-marking Effort for Networking Children’s Hospitals has been providing pediatric benchmarking data on performance indicators. Collaboration between NACHRI’s PPN and the MMP BENCH project presented an opportunity to couple the clinical expertise of PPN members in stewarding appropriate use of antimicrobial agents with the commitment to improve vancomycin practices made by hospital management and administrators involved in MMP’s BENCH. The collaboration also expanded the number of hospitals available to participate in the vancomycin study and optimized the use of hospital resources.

**METHODS**

The PPN conducted 2 studies of vancomycin usage. Survey I was distributed in October 1999 to 65 hospitals. Vancomycin control programs and measures taken to improve vancomycin use were reported and summarized.

Survey II was conducted 6 months following Survey I during May through August 2000. The objectives of this survey were to determine the vancomycin use patterns among inpatient services at children’s hospitals, to determine why physicians initiate and discontinue vancomycin, and to identify priority areas for intervention. All PPN hospitals were invited to participate in the
survey. Hospital personnel were asked to enroll prospectively the first 25 consecutive patients for whom vancomycin was prescribed during a 1-month period. Subjects were identified by vancomycin orders submitted to the hospital pharmacy. A 2-part questionnaire was distributed to participating hospitals. Part 1 was completed by pharmacy or infection control personnel. Demographic information on subjects included admission date, date of birth, hospital ward, and medical/surgical specialty physician ordering vancomycin. Underlying host factors, route of administration, length of therapy, and factors leading to discontinuation of vancomycin were also recorded. Part 2, completed by the physician who prescribed the vancomycin, included questions to determine the reasons vancomycin was prescribed. The 3 major categories for use included drug allergy, prophylaxis, or therapy. Factors that led to vancomycin use and laboratory results available at the time vancomycin was initiated were recorded. Based on physician responses, vancomycin use was classified as follows: prophylactic use—physician recorded indication as prophylaxis; empiric use—vancomycin administered before any positive culture results were available; therapeutic use—vancomycin initiated after positive culture results were available. Data were entered into a computerized database and analyzed using Epi-Info Version 6 software (Epidemiology Program Office, CDC, Atlanta, GA). Descriptive statistics were calculated, including the mean, median, and range.

RESULTS

Survey I
Personnel at 55/65 (85%) PPN hospitals responded to the first survey addressing current vancomycin control policies; 41 (75%) reported that they had implemented ≥1 measure to improve vancomycin use (Table 1). Although the specific components of vancomycin control policies varied among hospitals, personnel at 29 facilities (53%) had instituted ≥3 measures. Fifteen percent reported 2 measures, 34% 3 measures, 20% 4 measures, 10% 5 measures, and 6% 6 measures. The most frequent measures reported were practice guidelines (56%), education (49%), and automatic stop orders (44%).

Survey II
Personnel at 22 hospitals, 18 US hospitals, and 1 hospital each from Canada, Brazil, Australia, and Switzerland responded to the second survey. Data from 416 completed questionnaires were analyzed. The number of vancomycin courses reported from each hospital during the study period ranged from 2 to 25 (median = 12). Duration of vancomycin therapy ranged from 1 to 42 (median = 4) days. Age of patients ranged from newborn to 20 (median = 2) years. Duration of hospital stay before vancomycin initiation ranged from 0 to 226 (median = 4) days.

Vancomycin was prescribed because of β-lactam drug allergy in 26 (6%) patients. Prophylactic use included 51 (12%) episodes of surgical prophylaxis and 5 nonsurgical courses. The surgical procedures prophylaxed were ventricular peritoneal shunt insertion (18), other neurosurgery (10), cardiac surgery (12), other surgery (8), or intravascular catheter placement (3). For surgical prophylaxis, the number of doses ranged from 1 to 30 (median = 4). Duration of surgical prophylaxis ranged from 1 to 15 days (median = 2). One quarter of the patients received surgical prophylaxis for >2 days.

Of the therapeutic courses of vancomycin prescribed, 71 (17%) patients were neonates with clinical sepsis, 52 (13%) had fever with neutropenia, 49 (12%) had fever of unknown origin, 36 (9%) had positive blood cultures, 33 (8%) had pneumonia, 21 (5%) had meningitis, 9 (2%) had necrotizing enterocolitis, 8 (2%) had ventricular shunt infections, 6 (1%) had surgical site infections, 6 (1%) had cellulitis, 5 (1%) had catheter exit site infections, 5 (1%) had peritonitis, 4 (1%) had *Clostridium difficile* gastroenteritis, and 35 (8%) had other miscellaneous infections.

Physicians reported the following clinical factors that led to vancomycin use: vascular catheter in place (188, 45%), underlying diagnosis (179, 43%), severity of illness (96, 23%), uncertainty about diagnosis (51, 12%), unresponsive to current antibiotics (40, 10%), implant infections (13, 3% [neurosurgical shunts, joint prostheses, lumbar cerebrospinal fluid drain, ear tubel], or medical/legal concerns (1, 0.2%).

For 360 patients, microbiology results were available at the time vancomycin was prescribed: 85 (24%) patients had positive blood cultures, 45 (13%) patients had other positive cultures, 37 (10%) patients had positive Gram stains, and 29 (8%) patients had a resistant organism isolated.

Neonatologists were responsible for 27% of all orders to initiate vancomycin, followed by hematologists/oncologists (20%), surgeons (16%), general pediatricians (13%), intensivists (11%), or medical specialists (11%; Table 2). With the exception of surgeons, most therapy was empiric. Almost half (48%) of the patients were in an intensive care unit when vancomycin was prescribed; 117 (28%) were neonatal intensive care unit (NICU) patients and 79 (19%) were pediatric intensive care unit patients. Hematology/oncology units accounted for 19% of prescriptions and general pediatrics 16%.

We then evaluated the length of therapy categorized by clinical outcome. If cultures were negative or alternative antibiotics were initiated based on culture results, vancomycin was administered for a median of only 3 days (Table 3). Length of therapy was prolonged when the illness resolved without confirmation of a microbiologic diagnosis (median = 7 days) or when a therapeutic course was completed (median = 9 days). Approval for therapy was denied in only 1 patient, but vancomycin was administered for 4 days to that patient.

When vancomycin use by duration and clinical syndrome was evaluated, neonatal sepsis was
treated for 2 to 25 days (median = 6), fever/neutropenia 1 to 42 days (median = 3), fever of unknown origin 1 to 21 days (median = 3), pneumonia 1 to 13 days (median = 5), meningitis 1 to 34 days (median = 2), necrotizing enterocolitis 3 to 17 days (median = 10), ventricular shunt infection 1 to 26 days (median = 10), wound infection 1 to 8 days (median = 2), cellulitis 2 to 22 days (median = 2), catheter site infection 1 to 6 days (median = 2), and peritonitis 2 to 19 days (median = 5).

Many host factors were present that may have influenced the decision to administer vancomycin (Fig 1). Most notably, vascular catheters were present in 77% of patients. There were 128 peripheral catheters, 69 peripherally inserted central catheters, 53 arterial catheters, 46 central venous catheters, 41 implanted ports, 30 Broviac catheters, 40 Hickman catheters, and 13 umbilical catheters.

Recovery of blood culture pathogens resistant to β-lactams is another indication for possible vancomycin use. Such pathogens were reported frequently and included coagulase-negative staphylococcal species (CONS; 48), MRSA (5), ampicillin-resistant enterococcus (2), penicillin-resistant viridans streptococci (2), penicillin-resistant S. pneumoniae (1), or bacillus species (1). Information was not obtained to determine if blood cultures were drawn from central catheters or peripheral sticks.

**DISCUSSION**

Guidelines for the prevention of antimicrobial resistance in hospitals were issued by the Society of Health Care Epidemiology of America and Infectious

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**TABLE 2.** Use of Vancomycin by Service of Ordering Physician

<table>
<thead>
<tr>
<th>Ordering Physician/Service</th>
<th>Total No. of Vancomycin Courses</th>
<th>Prophylaxis</th>
<th>Empiric</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatology</td>
<td>112</td>
<td>7 (6%)</td>
<td>94 (84%)</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Hematology/oncology</td>
<td>81</td>
<td>1 (1%)</td>
<td>76 (94%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Surgery‡</td>
<td>68</td>
<td>35 (52%)</td>
<td>28 (41%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>General pediatrics</td>
<td>55</td>
<td>0 (0%)</td>
<td>53 (96%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Critical care medicine</td>
<td>47</td>
<td>6 (13%)</td>
<td>37 (79%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Other medical specialties§</td>
<td>47</td>
<td>8 (17%)</td>
<td>36 (77%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>4</td>
<td>0 (0%)</td>
<td>4 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>414</td>
<td>57 (14%)</td>
<td>328 (79%)</td>
<td>29 (7%)</td>
</tr>
</tbody>
</table>

*Surgical subspecialties: Neurosurgery (29), General (15), Cardiovascular (14), Orthopedic (5), Ophthalmology (1), Plastics (1), ENT (1), Urology (1), Transplant (1).

§Other Medical Specialties: Gastroenterology (14), Infectious Disease (13), Nephrology (5), Cardiology (4), Neurology (3), Pulmonology (3), Organ transplant (2), Endocrinology (1), Immunology (1), Palliative care (1).

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**TABLE 3.** Reasons for Vancomycin Discontinuation

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. of Patients</th>
<th>25th Percentile</th>
<th>Median</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic course completed</td>
<td>125</td>
<td>7</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Cultures negative</td>
<td>106</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Alternative antibiotic</td>
<td>75</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Prophylaxis completed</td>
<td>31</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Illness resolved without diagnosis</td>
<td>14</td>
<td>5</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Patient expired</td>
<td>13</td>
<td>2</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Approval denied</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

†Two of 416 surveys did not specify an ordering physician.

‡Surgical subspecialties: Neurosurgery (29), General (15), Cardiovascular (14), Orthopedic (5), Ophthalmology (1), Plastics (1), ENT (1), Urology (1), Transplant (1).

§Other Medical Specialties: Gastroenterology (14), Infectious Disease (13), Nephrology (5), Cardiology (4), Neurology (3), Pulmonology (3), Organ transplant (2), Endocrinology (1), Immunology (1), Palliative care (1).

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**Fig 1.** Host factors present at time of vancomycin administration.
Diseases Society of America in 1997.\textsuperscript{18} Additionally, optimal antimicrobial use is addressed in the Infectious Diseases Society of America guidelines for management of intravascular catheter infections\textsuperscript{25} and use of antimicrobial agents in neutropenic patients with cancer.\textsuperscript{26} These evidence-based consensus statements regarding judicious antibiotic use are based on experience in the adult population with occasional citations of published pediatric experiences. Despite the absence of pediatric-specific recommendations, in our first survey, we found that 3 of 4 children's hospitals have active programs to improve use of vancomycin. Over 80% of these PPN hospitals had initiated ≥1 intervention.

A cross-sectional survey of 47 hospitals participating in the CDC National Nosocomial Infections Surveillance project, Intensive Care Antimicrobial Resistance Surveillance Epidemiology study, was conducted in 1998 to evaluate antibiotic use policies.\textsuperscript{27} All hospitals had implemented active programs to improve antimicrobial use; 70% reported clinical practice guidelines, 60% had automatic stop orders, and 40% had restrictions on at least 1 antibiotic. Most restrictions were hospital-wide, but in 6 hospitals selected drugs were not restricted on the pediatric unit. Teaching hospitals were significantly more likely than other hospitals to restrict antibiotics. Our survey of personnel at children's hospitals, conducted in 1999, demonstrated lower levels of restrictive policies for vancomycin use; 55% reported practice guidelines, 40% had automatic stop orders, and 50% had implemented educational programs. Three quarters had implemented at least 1 activity to improve vancomycin use.

Studies to evaluate the outcome of antibiotic control measures were encouraged by the Society for Healthcare Epidemiology of America position paper on the Guidelines for the Prevention of Antimicrobial Resistance in Hospitals.\textsuperscript{18} Results of several published studies are noteworthy. Successful reduction of vancomycin use was demonstrated at 1 academic medical center where clinical pharmacists provided an educational note in the medical record following receipt of all vancomycin orders. Empiric vancomycin use improved from 20% to 90% adherence to established hospital guidelines within a 6-month period.\textsuperscript{28}

A study conducted in 1998 at a 150-bed tertiary care pediatric center reported on physician knowledge of appropriate vancomycin utilization.\textsuperscript{29} Questions on 18 clinical vignettes based on the CDC guidelines were answered by residents, fellows, and attending physicians from the Departments of Pediatrics, Surgery, and Emergency Medicine. Correct responses for vancomycin use did not vary with level of training or whether the physician was a pediatrician or nonpediatrician. Three quarters of the respondents gave correct answers. In our survey of prescribing physicians, most vancomycin therapy was used empirically (79%) or prophylactically (14%). Current practice guidelines support empiric use for suspected bacterial meningitis in children >1 month of age and for other central nervous system infections, ie, ventricular peritoneal shunt infections.\textsuperscript{16} However, only 5% of vancomycin courses that we evaluated were used to treat meningitis and 2% for ventricular shunt infections.

Nearly 25% of vancomycin use was for empiric therapy in neonates. Vancomycin is used in NICUs because of the high frequency of CONS bacteremia associated with indwelling catheters. A recent study has characterized the generally good outcomes that occur if vancomycin is not used as initial therapy for late-onset sepsis in the neonate.\textsuperscript{30} In this retrospective study, conducted in a tertiary care NICU from 1988–1997, 825 episodes of late-onset sepsis occurred in 536 infants. Although CONS accounted for 35% of all bacteremias, only 1% of these bacteremias resulted in significant clinical deterioration. During the period 1988 to 1994, empiric therapy was vancomycin and cefotaxime. From late 1994 through 1997, empiric therapy was changed to oxacillin and gentamicin. There was no difference in CONS bacteremia outcomes during these 2 periods. Similarly, Sanchez and colleagues\textsuperscript{31} demonstrated no change in outcome associated with a significant decrease in vancomycin use when the regimen for routine empiric treatment of suspected late-onset sepsis was changed from vancomycin and tobramycin to oxacillin or nafcillin and tobramycin.

A multicenter study conducted by the PPN in June 2000 to ascertain diagnostic and treatment practices for late-onset sepsis by neonatologists indicated that CONS was responsible for 54% of late-onset bacteremias in 1999.\textsuperscript{32} Thirty percent of NICU personnel reported patients with MRSA infections, 7% had ampicillin-resistant enterococci, but there were no reports of VRE. In this PPN survey, 27% of all vancomycin was administered to neonates; 94% of the use was for empiric therapy. Most neonatal units do not have endemic MRSA, or ampicillin-resistant enterococci.\textsuperscript{26,33} Thus, initial empiric Gram-positive coverage is directed against CONS, a low virulence pathogen. Furthermore, distinguishing contaminants from true pathogens by obtaining 2 blood cultures at the time of sepsis evaluation also decreases the use of vancomycin in the NICU.\textsuperscript{31,32} In contrast to the hospitals that responded to our Survey I, three quarters of the nurseries did not have a vancomycin restriction policy and more than half of the units used vancomycin as empiric therapy for late-onset sepsis. Therefore, the NICU represents a priority site for reducing use of vancomycin.

The second most frequent group receiving vancomycin in our survey was oncology patients with fever and neutropenia (13%). A European collaborative oncology trial compared ceftazidime and amikacin with a regimen of cefazidime, amikacin, plus vancomycin as initial empiric therapy of fever and neutropenia in cancer patients.\textsuperscript{34} A total of 747 patients were enrolled in the study. Gram-positive bacteremias responded clinically in 72% of patients treated with the vancomycin regimen compared with 43% of patients who did not receive vancomycin initially. However, no patients with Gram-positive bacteremia died within the first 3 days of empiric therapy. Nephrotoxicity was observed more frequently in patients treated with a vancomycin-con-
taining regimen. The authors concluded initial empirical use of vancomycin did not improve outcome in their neutropenic population and may be associated with increased adverse events. Recent guidelines for the use of antimicrobial agents in neutropenic patients with cancer published by the Infectious Diseases Society of America do not recommend routine use of vancomycin as initial therapy and delineate specific high-risk conditions under which empirical use of vancomycin is indicated.35

Neurosurgical or cardiovascular surgery patients received 80% of the prophylaxis courses of vancomycin. No clinical trials have demonstrated an improved outcome when vancomycin is used prophylactically compared with β-lactam antibiotics in these populations. Although CONS is a leading pathogen in neurosurgical shunt infections, infection rates vary widely among surgeons. A meta-analysis of prophylactic antibiotics showed a benefit in institutions with elevated baseline infection rates, but no protective effect if baseline infection rates were <5.5%.36 A 1995 survey on prophylactic antibiotic use in pediatric cardiovascular surgery at 43 centers37 reported that monotherapy with first or second-generation cephalosporins was used at 39 centers, vancomycin was used at 1 center, and 2 antibiotics were used at 4 centers. Prophylactic antibiotics were continued until thoracostomy tubes were removed in 29/43 (67%) centers, or mediastinal tubes were removed in 31/43 (72%) centers. In such patients, appropriate prophylactic vancomycin use would include a history of β-lactam allergy, a local outbreak of nosocomial MRSA postoperative infections, or for second operative procedures within a few days of the original prophylactic course of β-lactam antibiotics. In conclusion, vancomycin prophylaxis should not be used routinely for cardiovascular procedures.

Vancomycin use in PPN hospitals was strongly influenced by host factors, such as the presence of indwelling vascular catheters, neutropenia, or other immunocompromised states. Consistent implementation of recommended antisepsis of catheter insertion sites and recent advances in vascular catheter technology could markedly decrease the incidence of local exit site infections and catheter-associated bloodstream infections. Use of maximal sterile barrier precautions at the time of insertion of central venous catheters and removal of catheters when use is no longer indicated decreases the rates of Gram-positive bloodstream infections and therefore the need for vancomycin.38 Additionally, skin antisepsis with a 2% aqueous chlorhexidine gluconate preparation has been shown to lower bloodstream infection rates compared with 10% povidone-iodine or 70% alcohol.39 A 2% tincture of chlorhexidine skin antisepsis product was approved by the Food & Drug Administration in July 2000 and is now recommended for routine use in the HICPAC/CDC Guidelines for Prevention of Intravascular Device-Related Infections.38 Chlorhexidine/silver sulfadiazine and antibiotic (minocycline/rifampin) impregnated catheters have been demonstrated to decrease the rates of catheter colonization and catheter-associated infections.38 Over the last several years, smaller catheter lumens appropriate for pediatric use have been introduced in the United States. The role of these catheters in the pediatric population remains to be defined.

A strategy to discourage routine vancomycin therapy in neonates or febrile neutropenic oncology patients could substantially decrease vancomycin use in pediatric patients. Vancomycin could be added based on laboratory criteria, ie, positive buffy coat Gram-stain, blood culture report of Gram-positive cocci, cultures yielding resistant organisms, or clinical criteria, such as hypotension or disseminated intravascular coagulation.33

In our study, the median length of empiric therapy, if blood cultures were negative, was 3 days. With currently available automated systems, first identification of pathogens in positive blood cultures after 2 days is uncommon. A reasonable policy would be, if vancomycin were initiated as initial empiric therapy, that it be stopped after 2 days, if cultures remain negative and that true pathogens be distinguished from contaminants. Opportunities to limit the length of prophylactic therapy should be pursued. In our survey, median doses for surgical prophylaxis were 4, with a range up to 30. These patients with prolonged dosing probably illustrated an extension of prophylaxis to empiric therapy following the surgical procedure. Such an approach has been associated with increased antimicrobial resistance in adults.40

Our results are limited by the characteristics of hospitals participating in the PPN. Small hospitals and community hospitals with pediatric units are under-represented. To the degree that hospitals participating in these voluntary surveys differed from those that did not participate, our results may be biased. We have no reason to believe that vancomycin prescribing practices influenced a hospital’s decision to participate. However, it is possible that if hospitals believed their vancomycin use to be inappropriate, they may have declined to respond. The vancomycin prescribing survey was conducted during the summer months. A survey during the fall or winter may have identified increased vancomycin use for respiratory tract infections. Many centers submitted data for fewer than the 25 requested courses. Inappropriate vancomycin use that was prevented by restriction programs was not captured by our survey methodology. Surveying the prescribing physician’s motivation to institute vancomycin therapy was a unique feature of our study.

Given the difficulty in limiting vancomycin use in pediatric institutions, we will need to meet the challenge of defining stricter guidelines for new agents directed at Gram-positive organisms. Two recently introduced agents, quinupristin/dalfopristin41 and linezolid,42 may provide coverage for vancomycin-resistant staphylococci or enterococci. We must be more successful in controlling the use of these agents to limit the emergence of resistance and prolong their clinical usefulness.

Our data identify several areas for improving both vancomycin initiation and discontinuation: 1) surgical prophylaxis: restrict use of vancomycin for sur-
gal prophylaxis to patients with β-lactam allergies; discourage use for routine procedures unless MRSA is endemic within a given population; limit the number of doses to one dose 30 minutes before the incision and for prolonged procedures administer a second dose; 2) empiric therapy: reduce duration of empiric therapy pending laboratory culture results to 48 hours. Institutions should review protocols for empiric antimicrobial therapy and develop local, specialty-specific practice guidelines that delineate specific criteria for initiation of vancomycin. As computerized pharmacy order systems are introduced, appropriate algorithms will have a positive impact on vancomycin prescription patterns. Such physician feedback messages can be implemented before the institution of computerized physician order entry systems; 3) distinguish contaminants from pathogens by obtaining ≥2 blood cultures at the time of initial sepsis evaluation; and 4) improve intravascular catheter use and care to prevent catheter-associated Gram-positive bloodstream infections and decrease vancomycin use.

High priority areas for improved vancomycin use include NICUs and pediatric intensive care units, hematologic/oncology/hematopoietic stem cell transplant units, and surgical services. We encourage our pediatric colleagues to examine their vancomycin restriction policies and implement changes to improve the appropriateness of vancomycin use to decrease pressure for emergence of vancomycin-resistant pathogens. Further studies of methods that are effective to change prescribing patterns are warranted.

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