The Unique Issues of Outpatient Parenteral Antimicrobial Therapy in Children and Adolescents

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The decision to discharge a hospitalized child or adolescent to receive outpatient parenteral antimicrobial therapy (OPAT) is based on criteria very different from those concerning adults. Clinical studies of pediatric OPAT are sparse, as are pharmacokinetic data for antimicrobial agents in children. Other issues unique to children are requirements for special nursing and intravenous infusion skills, as well as the increase of complications. The psychological disadvantage of hospitalization in children, compared with adults, is great, and both populations are equally vulnerable to nosocomial infection, increasingly augmented by multidrug-resistant organisms. Although the relatively few clinical studies involving OPAT in children attest to its efficacy and safety, well-designed prospective trials and comprehensive cost-benefit analyses are still needed.

The advantages and principles of outpatient parenteral antimicrobial therapy (OPAT) in children and adolescents are generally similar to those in adults in terms of cost, safety, adherence, and convenience. In pediatric OPAT, however, both patient and caretakers are faced with a number of sometimes crucial differences. For example, clinicians may prescribe OPAT because of the inability of very young patients to take and retain oral agents; the very best pediatric antimicrobial is of no use to a child who cannot or will not swallow it. Thus, even if they have essentially the same infection, an adult may be discharged to home and prescribed a course of oral antibiotics, whereas a 5-year-old child may receive OPAT. Other issues unique to children and adolescents include the limited number of clinical studies of their response to OPAT, sparse child-specific pharmacokinetic data for antimicrobial agents that generally exclude children <6 months of age, known risks that exclude use of tetracyclines for children <8 years of age [1], requirements for special nursing and intravenous (IV) infusion skills, and increased risk of complications.

Seriously ill children who require hospitalization for treatment of invasive infections are at a great psychological disadvantage, compared with adults [2]. They have little understanding of the multiple procedures performed, most of which are threatening or painful. Moreover, nosocomial infections are a frequent problem in pediatric and adult wards and represent a serious problem significantly augmented by the increasing prevalence of multidrug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* [1,3, 4] and vancomycin-resistant enterococci [5].

The traditional concept that serious bacterial infections in young children must be treated with prolonged hospitalization for IV antibiotics has undergone re-evaluation [6]. Transition of antibiotic therapy from hospital to home may be accomplished in a number of ways. For some infections and for some older patients with many types of infection, parenteral antimicrobial therapy can be switched to treatment with oral agents (sequential antimicrobial therapy) after a patient shows improvement. For most very young patients, however, or for serious infections unresponsive to oral agents, continuation of the parenteral antimicrobial, either at home or with daily visits to a health care facility, remains the safest and most effective therapeutic course [6]. Because of the success of pediatric OPAT programs, outpatient therapy without initial hospitalization has been successful for some children [7].
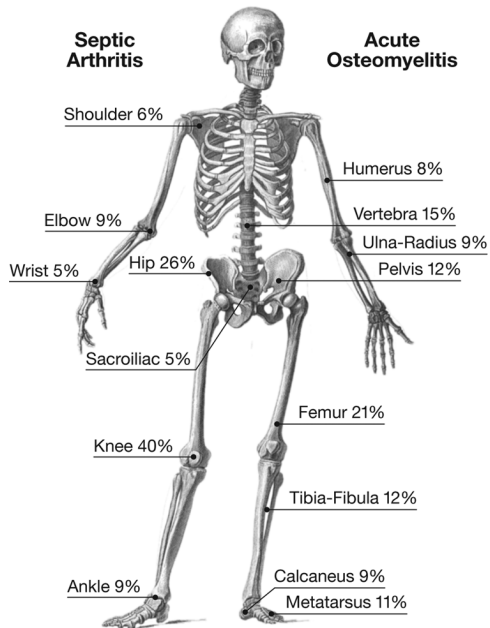
Figure 1. Sites of septic arthritis and acute osteomyelitis among 184 patients aged 3 months to 18 years. Adapted with permission from [14]. Maraqa NF, Gomez MM, Rathore MH. Outpatient parenteral antimicrobial therapy in osteoarticular infections in children. J Pediatr Orthop 2002; 22:506–10.

Although national guidelines for pediatric OPAT have not been formulated, most pediatric facilities with such programs have developed general medical criteria. Criteria in an early program [1] include identification of or high index of suspicion for the infecting organism; clinical response to IV or intramuscular antibiotic therapy; stable vital signs with no need for skilled nursing assessment of hydration, cardiorespiratory, neurologic, or wound healing status; and a very low risk for potential infectious complications. In short, every pediatric in-

fection can be treated, at least in part, on an ambulatory basis when factors, such as parenteral cooperation, geographic and transportation conditions, type of medical facility, and choice of appropriate antibiotics, are harmonized to attain this goal [8].

OPAT STUDIES IN CHILDREN AND ADOLESCENTS

To our knowledge, the first published report of OPAT was a 1974 study of outpatient IV medication administered to children with cystic fibrosis in their homes [9]. Studies during 1977–1978 that demonstrated the efficacy, safety, and cost-saving aspects of OPAT for serious infections were concerned primarily with adult patients, making only passing reference to children's issues [10–12]. The relatively few clinical trials devoted to children and adolescents that have been published to date conclude that OPAT is safe and effective for a number of serious bacterial infections. A 1984 study involved 89 patients aged 1.5–18 years who were selected from the population seen by the Infectious Disease Service of a community hospital and from patients referred to the service by other physicians [13]. Patients and/or their parents were instructed in the care of IV cannulas and aseptic administration of IV antibiotics. Some children had been hospitalized for long periods; others were admitted for the teaching phase only. When possible, patients were discharged with 20-gauge heparin locks in place. They returned to the program site every fourth day for physician evaluation, heparin lock changes, and laboratory studies for treatment efficacy and toxicity.

Most infections were in the bone and joints (53 cases), followed by respiratory tract infection (16), soft-tissue infection (9), genitourinary tract infection (4), surgical abdominal or pelvic infection (4), and septicemia (3) [13]. The most frequently encountered causative organism was *S. aureus,* which was found in 19 infections in the bone and joint, 5 in the

Table 1. Surgical Procedures Performed before Outpatient Parenteral Antimicrobial Therapy

Procedure	No. (%) of procedures		
	Acute osteomyelitis ($n = 116$)	Septic arthritis ($n = 42$)	Chronic osteomyelitis ($n = 26$)
Incision and drainage	46 (39.6)	3 (7.1)	12 (46.2)
Arthrocentesis	14 (12.1)	20 (47.6)	3 (11.5)
Arthrotomy	6 (5.2)	16 (38.1)	0 (0)
Bone aspiration	12 (10.3)	0 (0)	0 (0)
Bone biopsy	9 (7.8)	0 (0)	2 (7.7)
Sequestra removal	0 (0)	0 (0)	5 (19.2)
Not specified	29 (25)	3 (7.1)	4 (15.4)

NOTE. Reprinted with permission from [14]. Maraqa NF, Gomez MM, Rathore MH. Outpatient parenteral antimicrobial therapy in osteoarticular infections in children. J Pediatr Orthop 2002;22: 506–10.

Table 2. Causative Microorganisms and Frequency of Isolation

Organism	No. (%) of isolates	No. (%) of blood culture isolates
Gram-positive organisms		
Staphylococcus aureus	44 (36)	13 (56)
Coagulase-negative staphylococci	10 (8)	2 (8.7)
Corynebacterium species	6 (5)	1 (4.3)
Enterococcus species	4 (3)	0 (0)
Streptococcus pneumoniae	4 (3)	2 (8.7)
Group A *Streptococcus*	4 (3)	1 (4.3)
Group B *Streptococcus*	2 (2)	2 (8.7)
Clostridium species	2 (2)	0 (0)
Gram-negative organisms		
Pseudomonas species	17 (14)	0 (0)
Escherichia coli	6 (5)	0 (0)
Enterobacter species	6 (5)	0 (0)
Serratia species	4 (3)	0 (0)
Klebsiella species	3 (3)	0 (0)
Proteus species	3 (3)	0 (0)
Bacteroides species	2 (2)	0 (0)
Salmonella species	2 (2)	1 (4.3)
Kingella kingii	1 (1)	1 (4.3)
Morganella morgagni	1 (1)	0 (0)
Veillonella species	1 (1)	0 (0)
Acinetobacter species	1 (1)	0 (0)
Haemophilus influenzae	1 (1)	0 (0)

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respiratory tract, 2 in soft tissue, and 1 in the abdomen or pelvis and in 1 case of sepsis. Complications were divided into 3 categories: infiltrated or nonfunctional cannulae requiring unscheduled restarts, clinically diverse drug experiences, and laboratory abnormalities. Thirty-one patients (35%) required extra visits to the outpatient clinic for IV restarts, compared with 58 patients who had changes made only at scheduled visits. No statistically significant difference was found in the frequency of unscheduled heparin lock restarts for patients older or younger than the median age of 12 years. Adverse clinical and laboratory events occurred in patients receiving OPAT at a frequency commensurate with that among hospitalized patients. The investigators concluded that OPAT can provide a successful, safe, and cost-effective alternative to inpatient care under conditions of diligent patient screening and physician-centered follow-up [13].

Most later reports of OPAT for children involved the treatment of specific infections (eg, osteoarticular infections [14, 15], appendicitis [16], otitis media [7, 17, 18], and meningitis [19–24]), catheter-related complications [25, 26], adverse drug reactions [25], and specific antibiotic agents [17]. A number of studies of OPAT in children with cystic fibrosis [9, 27–30]

and with cancer [31–33] have been published but are not considered here.

Osteoarticular infections. Most pediatricians and pediatric infectious diseases specialists have or will have some experience with OPAT in the treatment of osteoarticular infections. During the past few decades, management of these challenging infections has shifted from hospital to outpatient settings, most often to the home, resulting in studies of patients aged 2–94 years [34–36]. Few involved children and adolescents specifically; however, in a study that did, investigators used a database an a Florida university-affiliated children's hospital of patients aged 3 months to 18 years who had received OPAT. Of 179 patients, 116 had acute osteomyelitis, 42 had septic arthritis, and 26 had chronic osteomyelitis (Figure 1) [14]. Table 1 shows the surgical procedures performed before patients were discharged to receive OPAT [14].

Gram-positive organisms were the most frequently isolated pathogens, with *S. aureus* in 36% and coagulase-negative staphylococci in 9% of infections (Table 2) [14]. OPAT was delivered through central venous lines (110), peripherally inserted central catheters (PICCs; 71), and peripheral cannulas (3). The type and frequency of catheter-related complications are shown in Table 3 [14]. On the basis of this review, in OPAT courses with a predicted duration of >2 weeks, central venous catheters (CVCs) may be associated with fewer mechanical and local infectious complications. However, considerations of safety in placing a PICC, compared with a central venous line, which requires surgery and general anesthesia, favors selection of the former. Antibiotic-associated complications are listed in Table 4 [14].

Clinical cure occurred in 97% of 172 evaluable osteoarticular infections [14]. The investigators conclude that OPAT can be

Table 3. Catheter-Related Complications

Complication	Complication rate, cases per 1000 catheter-days		
	All	CVL	PICC
Mechanical	6.3	4.2	10.6
Dislodgment	2.7	2.6	2.9
Occlusion and/or clotting	0.6	0.5	1.0
Malfunction	0.8	0.2	1.9
Leakage	0.5	0.2	1.0
Infiltration	0.2	0	0.5
Pneumothorax	0.2	0	0.5
Infectious	2.7	2.8	2.4
Local infection	2.1	2.4	1.4
Bacteremia	0.6	0.5	1.0
Total (*n* = 57)	9.0	6.6	13.9

NOTE. Reprinted with permission from [14]. Maraqa NF, Gomez MM, Rathore MH. Outpatient parenteral antimicrobial therapy in osteoarticular infections in children. J Pediatr Orthop 2002;22:506–510. CVL, central venous line; PICC, peripherally inserted central catheter.

Table 4. Antimicrobial-Associated Complications during Outpatient Parenteral Antimicrobial Therapy

Adverse drug reaction	No. (%) of cases ($n = 60$)[a]
Rash	33 (37.5)
Neutropenia[b]	28 (31.8)
Hepatotoxicity[c]	11 (12.5)
Fever	6 (6.8)
Diarrhea	5 (5.7)
Others[d]	5 (5.7)

NOTE. Adapted with permission from [14]. Maraqa NF, Gomez MM, Rathore MH. Outpatient parenteral antimicrobial therapy in osteoarticular infections in children. J Pediatr Orthop 2002;22:506–510.

[a] Some patients had >1 simultaneous adverse reaction.

[b] Absolute neutrophil count <1000 cells/mm³.

[c] Aspartate aminotransferase and alanine aminotransferase levels greater than twice the upper range of normal.

[d] Chest pain, shortness of breath, cyanosis, headache, and/or unknown.

used to manage these infections in children without compromising outcome. They emphasize the importance of a team approach in which caregivers are active participants in management and a supportive medical team is accessible at all times.

Sequential IV-oral antibiotic therapy has been used in the management of uncomplicated bone and joint infections in children [15, 37–39]. The advantages of switching to oral therapy include a shorter hospital stay and lower cost [14]. However, as noted above, this mode of therapy requires complete cooperation of the child and his or her caregivers. Moreover, to achieve a successful outcome, an oral antibiotic must have good penetration into the bone and synovium, attaining concentrations greater than needed to inhibit growth of the infecting organism. Thus, it has been suggested that oral therapy should be used only when the infecting organism is available for serum bactericidal titers [37].

For example, 22 children with acute hematogenous osteomyelitis (proven or presumed to be due to *S. aureus*) were treated with an IV antibiotic for 14 days, until fever had resolved, and then were switched to an oral agent [40]. Oral doses were adjusted so that a peak serum bactericidal titer against *S. aureus* of ≥1:16 and a trough serum bactericidal titer of ≥1:2 were obtained in most children. No recurrences occurred.

In a study that compared oral and IV antibiotic regimens in children with osteomyelitis and/or septic arthritis, all 15 patients were started on standard IV therapy; 7 patients were started on oral antibiotics within 72 h [15]. Oral doses were adjusted to achieve a peak serum bactericidal titer of ≥1:8 against individual patients' own pathogens. There were no treatment failures or relapses during a 12-month follow-up period. In another study involving 123 pediatric patients in Taiwan with acute hematogenous osteomyelitis and/or septic

arthritis, serum bactericidal titers were obtained for 19 (15%) of the patients [41]. Although there was no difference between median duration of hospitalization and antibiotic treatment, significantly more patients without serum bactericidal titers than patients with serum bactericidal titers (7 vs 0) had symptom relapse requiring rehospitalization.

The etiologic agent has become less of an issue for many pediatric infectious diseases specialists, however, who now feel that the decision to switch to an oral agent should be based on how well patients are doing while receiving parenteral antimicrobial therapy in the hospital. Again, the limiting factor may actually be the ability of the patient to take the antibiotic or of the parent to give the antibiotic. A retrospective cohort study involving 1969 children with acute osteomyelitis at 29 children's hospitals in the United States from 2000 through 2005 found that there was no difference in treatment failure between patients who received prolonged antimicrobial IV treatment ($n = 1021$) and those who were switched early to oral antimicrobial therapy ($n = 948$) [42]. There was also no clinical or demographic selection bias observed in the patients given either treatment. In addition, the authors of this study observed that "serum levels of oral antibiotics are no longer routinely measured" [42, p 641].

Complicated appendicitis. Children with a perforated or gangrenous appendix become clinically stable after surgical intervention and medical therapy but often remain in the hospital solely to complete parenteral antimicrobial therapy [16]. Several early studies suggested the safety and efficacy of OPAT for such patients after they are stabilized and receiving a regular diet, but specific information on outcome and cost savings was not provided [43–45]. With the advent of managed care, shorter courses of parenteral antimicrobial therapy and earlier hospital discharge are increasingly required for children with appen-
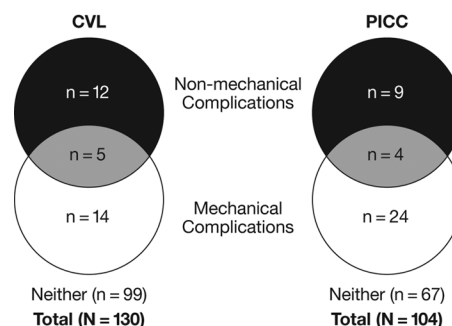

Figure 2. Venn diagrams of the number and type of complications that developed in 68 of 234 catheters. Nine catheters developed both mechanical (dislodgement or breakage) and nonmechanical (including infectious) problems. Reprinted with permission from SAGE Publications ©2007 [26]. Hussain S, Gomez MM, Wludyka P, Chiu T, Rathore MH. Survival times and complications of catheters used for outpatient parenteral antimicrobial therapy in children. Clin Pediatr (Phila) 2007;46:247–251. CVL, central venous line; PICC, peripherally inserted central catheter.
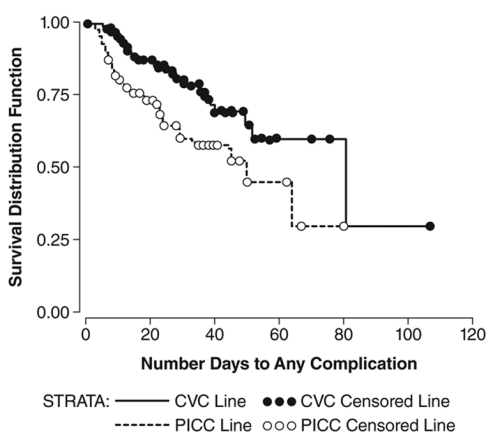
Figure 3. Survival curves showing the days to any catheter-associated complication, comparing the longevity of central venous catheters (CVCs) with that of peripherally inserted central catheters (PICCs). Mean survival time was 61 days (range, 1–107 days) for CVCs and 41 days (range, 0–80 days) for PICCs. Reprinted with permission from SAGE Publications ©2007 [26]. Hussain S, Gomez MM, Wludyka P, Chiu T, Rathore MH. Survival times and complications of catheters used for outpatient parenteral antimicrobial therapy in children. Clin Pediatr (Phila) 2007; 46:247–251.

dicitis. For those with complicated infections that require continuation of parenteral therapy, OPAT can be a safe, effective, and cost-effective alternative to continued hospitalization [16].

A 16-month, prospective study of OPAT in selected patients from 5 pediatric hospitals involved 87 children aged 1–17 years who were hospitalized with appendicitis complicated by generalized peritonitis or intraabdominal abscess [16]. Patients underwent operative appendectomy (78 patients) or only CT–guided or surgical drainage (9). Patients whose fever was improving and who were able to tolerate oral liquids were discharged to home for continuation of parenteral antimicrobial therapy, to be administered by a family member supervised by home care nurses. Patients were discharged on a mean of the fourth postoperative day and received ~4.5 days of OPAT with meropenem (20 mg/kg/dose every 8 h). Fifteen patients were discharged with peritoneal drains. Study personnel visited the home daily to collect data on adverse events, compliance, and resource use.

Six children were readmitted for complications, including bowel obstruction (4 children), intraabdominal abscess (1), and pleural effusion (1) [16]. A seventh patient developed a viral syndrome and was admitted for overnight observation. Rates of nonfunctional catheters were 9 cases per 100 days of outpatient peripheral catheter use (52 children) and 2.6 cases per 100 days of outpatient PICC use (22 children). No complications of IV access occurred among the 13 patients discharged with subcutaneously tunneled Silastic central catheters. No wound infections occurred during OPAT. Six children discontinued the study drug prematurely because of rash (4 children)

or diarrhea (2 children). All other patients recovered uneventfully. According to models in which each day of OPAT replaced a day of inpatient care, discharge to OPAT reduced hospitalization by ~42 days and saved a median of $2908 per patient [16].

Meningitis. Data on outpatient therapy of pediatric meningitis, most of which were published in the 1980s and 1990s, reported favorable results with OPAT use [19–24]. Therapy was given either at home, in the physician's office, or in a hospital ambulatory care department. One review suggested criteria for patients being considered for outpatient therapy [22] that included documentation of sterile cerebrospinal fluid from a repeat lumbar puncture 24–48 h after initiation of therapy, no seizures having occurred during the entire course of illness, that the patient should be taking fluids entirely by mouth, and that parents must have access to a telephone and transportation and be willing to stay at home to provide care and observation. It was also suggested that a consent form be obtained from parents that outlined the risks and responsibilities of outpatient therapy [22].

The Committee on Infectious Diseases of the American Academy of Pediatrics issued a report on the treatment of bacterial meningitis in 1988 that stated that "for a few patients with meningitis, alternative treatment regimens might be considered to shorten the duration of hospitalization and to provide completion of treatment at home" [46, p 906]. The report also established standards for physicians who provided the last few days of treatment for bacterial meningitis at home, including assurance that the child's clinical status is stable, that the parents are reliable and the child is cooperative, and that daily antibiotics can be administered and the child's clinical status can be assessed. However, the report also states that, "until there is additional information, the committee does not recommend early discharge from the hospital for home management of infants and children with bacterial meningitis" [46, p 906]. Furthermore, neither the American Academy of Pediatrics "Report of the Task Force on Diagnosis and Management of Meningitis" [47], published in 1986, nor the Academy's *Red Book* [48], published in 2006, addressed outpatient therapy for bacterial meningitis. In our practice, we discourage the use of OPAT for treatment of meningitis.

OPAT AND CATHETER COMPLICATIONS

Few data are available regarding catheter-related complications of OPAT during childhood. IV access used in pediatric OPAT includes peripheral IV catheters, midline catheters, implanted ports, tunneled CVCs, and PICCs. Recent advances in these catheters and in infusion devices now allow more complex therapies to be provided with less effort by parents or patients, resulting in the availability of OPAT to an increasing number of patients. However, a significant number of OPAT courses in

children are associated with catheter-related complications [14, 25, 49].

In a 5-year retrospective analysis involving children who received OPAT, 130 CVCs and 104 PICCs were used in patients aged 0–19 years (mean, 7.5 years) [26]. A complication was defined as mechanical if ≥1 catheter component malfunctioned at the time of its placement or during OPAT. All other complications were defined as nonmechanical, including those labeled infectious, the result of either confirmed microbiologic diagnosis or clinical suspicion, and those that were unknown, when patient records indicated only a nonspecific catheter-related complication. For purposes of analysis, when a catheter had >1 complication, time to development was based on the first complication noted.

A total of 77 complications occurred: 47 mechanical and 30 nonmechanical (Figure 2) [26]. Because of missing data, mean survival time to any complication was calculated for 128 CVCs and 100 PICCs (Figure 3) [26]. Mechanical complications were more likely to develop in PICCs than in CVCs. Of 47 mechanical complications, 14 were accidental dislodgement (7 CVCs and 7 PICCs). Of a total of 68 rehospitalizations required, 19 were exclusively for catheter replacement. Infections caused 25 of 30 nonmechanical complications; the most common was infection of the exit wound site. Mean survival time for CVCs was 66 days and for PICCs was 42 days.

Severe catheter-related complications occurred in 1 patients: one patient had pneumothorax at the time of PICC placement, and the other had hypotension and arrhythmia triggered by the position of the distal end of the PICC in the heart [26]. Although no clear guidelines exist for when to choose a CVC versus a PICC in pediatric OPAT, the investigators concluded that PICCs can be used to treat most common pediatric infections requiring OPAT and that CVCs appear to be a better choice for OPAT with a duration of >6 weeks.

CONCLUSION

Given reasonable medical criteria for hospital discharge, motivated and compliant parents, and skilled visiting pediatric nurses, a significant number of children with serious bacterial infections that require parenteral therapy can now be treated conveniently, safely, and effectively at home. Such therapy offers the potential for excellent medical treatment, reduced cost, and improved quality of life for sick children. The relatively few published studies to date attest to the efficacy and safety of OPAT for children and adults. Properly designed prospective clinical trials are still needed, however, as are pediatric guidelines similar to those available for adults. Also needed are studies of the impact of OPAT on patient and parent/caretaker quality of life and comprehensive cost-benefit analyses.

References

1. Hinckley J, Allen PJ. Community-associated MRSA in the pediatric primary care setting. Pediatr Nurs **2008**; 34:64–71.
2. Bradley JS. Outpatient parenteral antibiotic therapy: management of serious infections. Part I: Medical, socioeconomic, and legal issues. Pediatric considerations. Hosp Pract (Off Ed) **1993**; 28(suppl 1):28–32.
3. McDonald JR, Carriker CM, Pien BC, et al. Methicillin-resistant *Staphylococcus aureus* outbreak in an intensive care nursery: potential for interinstitutional spread. Pediatr Infect Dis J **2007**; 26:678–683.
4. David MZ, Crawford SE, Boyle-Vavra S, Hostetler MA, Kim DC, Daum RS. Contrasting pediatric and adult methicillin-resistant *Staphylococcus aureus* isolates. Emerg Infect Dis **2006**; 12:631–637.
5. Benson L, Sprague B, Campos J, Singh N. Epidemiology of infection and colonization with vancomycin-resistant enterococci and frequency of co-colonization with methicillin-resistant *Staphylococcus aureus* in children. Infect Control Hosp Epidemiol **2007**; 28:880–882.
6. Gutierrez K. Continuation of antibiotic therapy for serious bacterial infections outside of the hospital. Pediatr Ann **1996**; 25:639–645.
7. Dagan R, Fliss DM, Einhorn M, Kraus M, Lieberman A. Outpatient management of chronic suppurative otitis media without cholesteatoma in children. Pediatr Infect Dis J **1992**; 11:542–546.
8. Dagan R. How far can the paediatric patient with a serious infection be managed as an outpatient? J Hosp Infect **1995**; 30(suppl):172–178.
9. Rucker RW, Harrison GM. Outpatient intravenous medications in the management of cystic fibrosis. Pediatrics **1974**; 54:358–360.
10. Williams DN, Rehm SJ, Tice AD, Bradley JS, Kind AC, Craig WA. Practice guidelines for community-based parenteral anti-infective therapy. ISDA Practice Guidelines Committee. Clin Infect Dis **1997**; 25:787–801.
11. Antoniskis A, Anderson BC, Van Volkinburg EJ, Jackson JM, Gilbert DN. Feasibility of outpatient self-administration of parenteral antibiotics. West J Med **1978**; 128:203–206.
12. Stiver HG, Telford GO, Mossey JM, et al. Intravenous antibiotic therapy at home. Ann Intern Med **1978**; 89:690–693.
13. Goldenberg RI, Poretz DM, Eron LJ, Rising JB, Sparks SB. Intravenous antibiotic therapy in ambulatory pediatric patients. Pediatr Infect Dis **1984**; 3:514–517.
14. Maraqa NF, Gomez MM, Rathore MH. Outpatient parenteral antimicrobial therapy in osteoarticular infections in children. J Pediatr Orthop **2002**; 22:506–510.
15. Kolyvas E, Ahronheim G, Marks MI, Gledhill R, Owen H, Rosenthall L. Oral antibiotic therapy of skeletal infections in children. Pediatrics **1980**; 65:867–871.
16. Bradley JS, Behrendt CE, Arrieta AC, et al. Convalescent phase outpatient parenteral antiinfective therapy for children with complicated appendicitis. Pediatr Infect Dis J **2001**; 20:19–24.
17. Esposito S, Noviello S, Ianniello F, D'Errico G. Ceftazidime for outpatient parenteral antibiotic therapy (OPAT) of chronic suppurative otitis media due to *Pseudomonas aeruginosa*. J Chemother **2000**; 12:88–93.
18. Einhorn M, Fliss DM, Leiberman A, Dagan R. Otolaryngology and infectious disease team approach for outpatient management of serious pediatric infections requiring parenteral antibiotic therapy. Int J Pediatr Otorhinolaryngol **1992**; 24:245–251.

19. Waler, JA, Rathore MH. Outpatient management of pediatric bacterial meningitis. Pediatr Infect Dis J 1995; 14:89–92.

20. Bradley JS. Outpatient parenteral antibiotic therapy: management of serious infections. Part II: Amenable infections and models for delivery. Meningitis Hosp Pract (Off Ed) 1993; 28(suppl 2):15–19.

21. Powell KR, Mawhorter SD. Outpatient treatment of serious infections in infants and children with ceftriaxone. J Pediatr 1987; 110:898–901.

22. Steele R, Marcy S. Outpatient management of bacterial meningitis. Pediatr Infect Dis J 1989; 8:258–260.

23. Bradley JS, Ching DK, Phillips SE. Outpatient therapy of serious pediatric infections with ceftriaxone. Pediatr Infect Dis J 1988; 7:160–164.

24. Nelson JD. Options for outpatient management of serious infections. Pediatr Infect Dis J 1987; 6:603–606.

25. Gomez M, Maraqa N, Alvarez A, Rathore M. Complications of outpatient parenteral antibiotic therapy in childhood. Pediatr Infect Dis J 2001; 20: 541–543.

26. Hussain S, Gomez MM, Wludyka P, Chiu T, Rathore MH. Survival times and complications of catheters used for outpatient parenteral antibiotic therapy in children. Clin Pediatr (Phila) 2007; 46:247–251.

27. Donati MA, Guenette G, Auerbach H. Prospective controlled study of home and hospital therapy of cystic fibrosis pulmonary disease. J Pediatr 1987; 111:28–33.

28. Kane RE, Jennison K, Wood C, Black PG, Herbst JJ. Cost savings and economic considerations using home intravenous antibiotic therapy for cystic fibrosis patients. Pediatr Pulmonol 1988; 4:84–89.

29. Gilbert J, Robinson T, Littlewood JM. Home intravenous antibiotic treatment in cystic fibrosis. Arch Dis Child 1988; 63:512–517.

30. Strandvik B, Hjelte L, Malmborg AS, Widén B. Home intravenous antibiotic treatment of patients with cystic fibrosis. Acta Paediatr 1992; 81: 340–344.

31. Shemesh E, Yaniv I, Drucker M, et al. Home intravenous antibiotic treatment for febrile episodes in immune-compromised pediatric patients. Med Pediatr Oncol 1998; 30:95–100.

32. Hooker L, Kohler J. Safety, efficacy, and acceptability of home intravenous therapy administered by parents of pediatric oncology patients. Med Pediatr Oncol 1999; 32:421–426.

33. Wiernikowski JT, Rothney M, Dawson S, Andrew M. Evaluation of a home intravenous antibiotic program in pediatric oncology. Am J Pediatr Hematol Oncol 1991; 13:144–147.

34. Ingram C, Eron LJ, Goldenberg RI, et al. Antibiotic therapy of osteomyelitis in outpatients. Med Clin North Am 1988; 72:723–738.

35. Tice AD. Outpatient parenteral antimicrobial therapy for osteomyelitis. Infect Dis Clin North Am 1998; 12:903–919.

36. Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. J Antimicrob Chemother 2003; 51:1261–1268.

37. Tetzlaff TR, McCracken GH Jr, Nelson JD. Oral antibiotic therapy for skeletal infections of children. II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr 1978; 92:485–490.

38. Green NE, Edwards K. Bone and joint infections in children. Orthop Clin North Am 1987; 18:555–576.

39. Reid S, Bonadio W. Feasibility of short-term outpatient intravenous antibiotic therapy for the management of infectious conditions in pediatric patients. Am J Emerg Med 2006; 24:839–842.

40. Prober CG, Yeager AS. Use of the serum bactericidal titer to assess the adequacy of oral antibiotic therapy in the treatment of acute hematogenous osteomyelitis. J Pediatr 1979; 95:131–135.

41. Kao HC, Huang YC, Chin CH, et al. Acute hematogenous osteomyelitis and septic arthritis in children. J Microbiol Immunol Infect 2003; 36: 260–265.

42. Zaoutis T, Localio AR, Leckerman K, et al. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics 2009; 123:636–642.

43. Stovroff MC, Totten M, Glick PL. PIC lines save money and hasten discharge in the care of children with ruptured appendicitis. J Pediatr Surg 1994; 29:245–247.

44. Warner BW, Kulick RM, Stoops MM, Mehta S, Stephan M, Kotagal UR. An evidence-based clinical pathway for acute appendicitis decreases hospital duration and cost. J Pediatr Surg 1998; 33:1371–1375.

45. Firilas AM, Higginbotham PH, Johnson DD, Jackson RJ, Wagner CW, Smith SD. A new economic benchmark for surgical treatment of appendicitis. Am Surg 1999; 65:769–773.

46. American Academy of Pediatrics Committee on Infectious Diseases. Treatment of bacterial meningitis. Pediatrics 1988; 81:904–907.

47. Klein JO, Feigin RD, McCracken GH Jr. Report of the Task Force on Diagnosis and Management of Meningitis. Pediatrics 1986; 78:959–982.

48. Report of the Committee on Infectious Diseases. In: Red Book. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006.

49. Hoffman-Terry ML, Fraimow HS, Fox TR, Swift BG, Wolf JE. Adverse effects of outpatient parenteral antibiotic therapy. Am J Med 1999; 106: 44–49.