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Optimizing antimicrobial therapy in children

Sarah S. Long*

Drexel University College of Medicine, Chief, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, PA, USA

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Summary Management of common infections and optimal use of antimicrobial agents are presented, highlighting new evidence from the medical literature that enlightens practice. Primary therapy of staphylococcal skin abscesses is drainage. Patients who have a large abscess (>5 cm), cellulitis or mixed abscess–cellulitis likely would benefit from additional antibiotic therapy. When choosing an antibiotic for outpatient management, the patient, pathogen and *in vitro* drug susceptibility as well as tolerability, bioavailability and safety characteristics of antibiotics should be considered. Management of recurrent staphylococcal skin and soft tissue infections is vexing. Focus is best placed on reducing density of the organism on the patient's skin and in the environment, and optimizing a healthy skin barrier. With attention to adherence and optimal dosing, acute uncomplicated osteomyelitis can be managed with early transition from parenteral to oral therapy and with a 3–4 week total course of therapy. Doxycycline should be prescribed when indicated for a child of any age. Its use is not associated with dental staining. Azithromycin should be prescribed for infants when indicated, whilst being alert to an associated ≥2-fold excess risk of pyloric stenosis with use under 6 weeks of age. Beyond the neonatal period, acyclovir is more safely dosed by body surface area (not to exceed 500 mg/m^2/dose) than by weight. In addition to the concern of antimicrobial resistance, unnecessary use of antibiotics should be avoided because of potential later metabolic effects, thought to be due to perturbation of the host's microbiome.

Bugs and drugs: optimizing common use of antimicrobial agents

Management of common infections and optimal use of antimicrobial agents are presented, highlighting new evidence from the medical literature that enlightens practice.

Staphylococcus aureus

Management of staphylococcal skin and soft tissue infection (SSTI)

For purulent staphylococcal SSTIs, drainage is proven to be the optimal primary management.[1] For drained abscesses

* St. Christopher's Hospital for Children, 160 E. Erie Avenue, Section of Infectious Diseases, USA. Tel.: +1 215 427 5204; fax: +1 215 427 8389.
E-mail address: sarah.long@drexelmed.edu

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<5 cm, antibiotic therapy is controversial. For larger drained abscesses, cellulitis, mixed abscess—cellulitis, or for patients with systemic illness, antibiotic therapy is prescribed. Although geographically variable, approximately 90% of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA) are susceptible to clindamycin and >90% are susceptible to TMP—SMX *in vitro*. Favorable absorption, bioavailability and safety support their use among limited choices for outpatient therapy for MRSA.

TMP—SMX inhibits consecutive steps in the synthesis of folic acid and thymidine; bacteria that depend on synthesis are susceptible. During conditions of *in vitro* growth, *S. aureus* can appear susceptible but during infection may bypass folic acid synthesis, acquiring necessary growth factors from the environment. Retrospective studies of treatment effectiveness of clindamycin compared with trimethoprim—sulfamethoxazole (TMP—SMX) are inconclusive, some studies suggesting suboptimal outcomes for TMP—SMX.

The results of a long-awaited U.S. National Institutes of Health sponsored multicenter, prospective, randomized double-blind superiority trial of clindamycin versus TMP—SMX for uncomplicated skin infections became available in 2015.[2] Entry required ≥2 of the following findings at the site of skin infection: erythema, induration, warmth, purulent drainage or tenderness. Adults with temperature >38.5 °C and infants with temperature >38 °C were excluded, as were ill patients and those with underlying conditions (including obesity) or recent surgery. Infections were categorized and results were stratified as abscess alone, cellulitis alone or mixed abscess—cellulitis lesions. All abscesses were drained. Adult doses of study medications (with adjustment for children) were TMP—SMX (80 mg trimethoprim), 2 tablets bid plus 2 placebo tablets midday; or clindamycin (150 mg), 2 tablets tid. Treatment course was 10 days. Primary outcome was clinical cure 7—10 days after completion of therapy.

Results showed that 264 clindamycin-treated and 260 TMP—SMX treated subjects were well matched: abscess only (30% and 31%, respectively), cellulitis only (52% and 55%), and mixed abscess—cellulitis (18% and 14%). Thirty percent of subjects were <18 years old. Approximately one-half of patients had a positive culture; both groups having 32% with MRSA, 10% with MSSA, and clindamycin resistance in 4% of MRSA and 1% of MSSA. Clinical cure was almost identical, i.e., 90% for clindamycin and 88% for TMP—SMX treated patients.

The study and results certainly are useful, but have limitations. Culture was not performed or was negative in approximately 50% of cases. The relative contribution of *Streptococcus pyogenes* to cases (especially of cellulitis) and performance of TMP—SMX in such cases were not evaluable by an adequate clinical or culture-proven sample size. The clinical cure rate for clindamycin in proven clindamycin-susceptible versus clindamycin-resistant staphylococcal infections was 92% and 73%, respectively ($P = .06$). Although sample size for this subgroup analysis was small, the findings raise the possibility of a 73% rate of spontaneous resolution of infection in subjects entered into the study. Although this in itself may have clinical meaning, i.e., antibiotic treatment may not be necessary in the majority of patients as selected in this study and who have an abscess drained, the reduced sample size of subjects who likely would benefit from therapy might preclude rigorous comparison of relative drug effectiveness.

There is no simple choice of the child who would benefit from antibiotic therapy after drainage of an abscess, or the single best drug, especially considering MRSA, cellulitis and the possibility of *S. pyogenes*. Each choice has advantages and disadvantages: TMP—SMX has *in vitro* activity against most MRSA but inferior anti-streptococcal effectiveness and infrequent but morbid drug-related events such as Stevens—Johnson syndrome; clindamycin has activity against ~90% MRSA and MSSA but the suspension has a disagreeable smell and taste; doxycycline has activity against most MRSA but use in children <8 years of age has been limited; levofloxacin has *in vitro* activity against many MRSA but organisms can develop resistance rapidly and use in children requires special consideration; linezolid has activity against "all" MRSA but is costly and has troublesome potential drug interactions and adverse events. Decisions must be made individually. Obtaining a culture and susceptibility testing are major assets in guiding management.

Management of recurrent staphylococcal SSTI

Systemic antibiotic therapy for first staphylococcal SSTI may reduce SSTI recurrences or delay time to recurrence.[3] The majority of patients with MRSA SSTIs or their family contact(s) or both will have recurrence(s)/occurrence(s) over months. Multiple studies have investigated relative effectiveness of antibiotics for therapy or decolonization, as well as topical treatments and environmental manipulations to prevent recurrence or spread of staphylococcal SSTIs. The problem reflects the pathogen's capability of persistence on the host's skin and mucosa, high transmissibility, and persistence in the environment. No final solution is within sight. A few studies are highlighted to emphasize the complexity of issues and to point to practical attempts for containment.

In a Tennessee retrospective study of treatment of first episode of SSTI in approximately 6400 children whose abscess was drained, the odds ratio for recurrence within one year, considering clindamycin as the standard, was 2.23 (95% CI, 1.71—2.9) for a beta-lactam agent, and 1.92 (95% CI, 1.49—2.47) for TMP—SMX.[4] In a St. Louis prospective study of management with nasal mupirocin twice daily plus use of chlorhexidine body wash, recurrence rate of SSTI was 72% when the index child alone performed the treatment, and fell to 52% when household members also performed the regimen ($P = .02$).[5] An added insight was that final *S. aureus* carriage in index patients (approximately 50%) was similar in both treatment arms, suggesting that the goal of decolonization is elusive. The same investigators searched households for bacterial reservoirs in a cohort of children with MRSA SSTIs.[6] Swabbing 21 high-touch surfaces in 50 households, MRSA was detected in one-half of houses. Patient bed linens, electronic remote control devices and bathroom towels were top reservoirs. Testing of environmental and patient MRSA isolates showed strain-relatedness in 40% of houses. In a prospective Los Angeles—Chicago longitudinal study of 330 patients with *S. aureus* SSTI and their 588 family contacts, recurrence rate

of SSTIs in index cases was 39% at 3 months and 51% at 6 months.[7] Contamination of fomites had statistically significantly increased odds ratios (1.39—1.88) for both recurrence of SSTI in the index patient and occurrence in family members.

Table 1 summarizes this author's current approach to management. Many patients come to referral for recurrent abscesses without proof of etiology or susceptibility testing of an isolate. Since spontaneous resolution of episodes following drainage is typical, history of receipt of a specific antibiotic does not prove etiology or drug activity against the pathogen. A single course of therapy with an agent proven to be active against the patient's pathogen is prescribed, because this may modestly delay or reduce recurrences.[3] Then, efforts are focussed on 1) reducing the density of organisms on the skin and in the environment; and 2) improving condition of the skin as a barrier to invasion e.g., by aggressive management of eczema or diaper rashes, and eliminating body shaving in girls and in male athletes.

Therapy of acute osteomyelitis

Multiple retrospective studies in Europe over decades showed that management of acute osteomyelitis with early transition from parenteral to oral antibiotic therapy (after defervescence, clinical improvement and reduction in biomarkers of inflammation), and a total 3-week course of therapy was safe.[8] The strategy of oral therapy for osteomyelitis was partially adopted in the U.S. in the 1970s—1980s, only when bacterial etiology was proven, the clinical course was uncomplicated, adherence to oral therapy was highly likely, the pathogen was susceptible *in vitro* to a tolerable and bioavailable agent, and an adequate serum cidal level was proven.[9] In this test, a serum sample was collected 1 h after oral administration of the chosen antibiotic, diluted, and added to standard broth inoculum of the patient's pathogen. A 99.9% bactericidal effect *in vitro* of $\geq$1:4 dilution of serum was considered acceptable. Because performance of the serum cidal assay was labor intensive and laboratory quality control was not possible this test was abandoned. Additionally, MRSA ascended as a common etiologic agent of acute osteomyelitis in the 1990s. Published U.S. and European experience with oral therapy had not included MRSA osteomyelitis, which frequently is complicated by thrombosis, necrosis, delayed sterilization and for which choices for oral therapy are limited. Concurrently, percutaneous central venous catheters (PICCs) were introduced for outpatient use, facilitating prolonged intravenous therapy.

In 2015, Keren et al. published a case series comparing effectiveness of intravenous versus oral antibiotic therapy for postdischarge treatment of acute osteomyelitis.[10] Using the Pediatric Health Information System (PHIS) administrative (billing) database of 38 freestanding U.S. children's hospitals, investigators entered cases of first episode of acute osteomyelitis in patients 2 months to 18 years of age without underlying conditions who were admitted through the hospitals' Emergency Departments (EDs). Investigators augmented billing data by capturing Microbiology Laboratory reports, antibiotic(s) administered at discharge and ED visits after discharge. They performed propensity-score matching of cases discharged receiving antibiotic(s) intravenously versus orally. Primary outcome was return to the ED due to an osteomyelitis-related problem (treatment failure), and secondary outcome was return due for a drug- or PICC-related problem.

More than 8000 cases with the diagnosis of acute osteomyelitis were reviewed to achieve a final cohort of 2060 patients. Oral drugs used at discharge generally were clindamycin or cephalexin, and intravenous drugs were clindamycin, cefazolin, ceftriaxone or vancomycin. Groups were evenly matched for sex, ages 5 through 12 years, and government insurance. Treatment failure was similar for those receiving antibiotic IV (6%) or orally (5%). Return to ED for an adverse drug event was similar (4% vs 2%, respectively), but 15% of patients treated intravenously had return ED visits for PICC-related problems. Administrative "big data" can have big trade-offs of incompleteness.[11] Despite propensity scoring, patients treated orally may have had predictably better outcomes, e.g., no bacteriologic confirmation in 50% treated orally versus 35% treated intravenously, MSSA 29% versus 38%, MRSA 14% versus 19% and osteotomy performed in 35% versus 42%, respectively. There also was uneven distribution of treatment across hospitals, with some "almost never" and some "almost always" choosing oral mode of therapy.

Taken together, decisions on agent of choice, delivery and duration of therapy seem to be made optimally on a case-by-case basis, weighing multiple patient, family, pathogen and drug factors as well as risk of prolonged PICC placement and consequences of failure. It should be remembered that when serum cidal concentrations were measured in the 1970s—1980s, dosage of an agent orally to

Table 1 The author's suggested management strategy to reduce recurrent staphylococcal skin infections.

- Prove bacteriology and antibiotic susceptibility.
- Everyone deserves one 14-day course of an active antibiotic. — First choice clindamycin if a susceptible pathogen.
- Decolonization is difficult. — Do not test for pathogen eradication.
- Focus on controlling density of contamination.
- Prescribe the following, to begin during the course of systemic antibiotic: — Mupirocin nasally bid for $\geq$5 days.
  - — Chlorhexidine washes/showers or dilute bleach bath: daily for the first week, and then twice weekly indefinitely.
  - — Blitz the bathroom: dispose of partially used products and clean all surfaces with bleach.
  - — Launder bed linens and clothes at high temperature, using bleach if possible.
  - — Decontaminate high touch surfaces: door knobs, hand held electronic devices, light switches/plates, etc.
  - — Aggressively manage skin conditions (eczema, diaper dermatitis).

achieve acceptable serum cidal level generally was ≥2-fold the usual dose (e.g., 100–150 mg/kg/day of cephalexin and ≥40 mg/kg/day of clindamycin) and drug was administered every 6 h.[9] It is our practice to continue antibiotic therapy in acute uncomplicated osteomyelitis for 10–14 days after all of the following: defervescence, observable resolution of pain on weight-bearing or use, and fall of CRP to <1 mg/dL.

Streptococcus pneumoniae

Reduced susceptibility of *Streptococcus pneumoniae* to beta-lactam antibiotics occurs when colonizing *S. pneumoniae* can persist in the nasopharynx under antibiotic pressure, through successive mutations.[12] Nonsusceptibility of *S. pneumoniae* began substantially in the 1990s, and continued during the PCV7 era, especially related to colonization advantage and mutation of *S. pneumoniae* serotype 19A and 6A. High-dose amoxicillin or amoxicillin-clavulanate 14:1 was adopted for outpatient empiric therapy for suspected pneumococcal infection, ceftriaxone plus vancomycin for suspected bacterial meningitis, and high-dose ampicillin or ampicillin–sulbactam for invasive infection outside the CNS. In 2014 and 2015, studies from the Americas, Europe and Israel documented decrease in incidence of otitis media in the PCV13 versus the PCV7 era.[13–16] In Israel, incidence of otitis media in children <2 years of age fell from 9.2 to 6.2 per 1000 population during the PCV7 era, to 2.1 per 1000 when >70% of children had received 2 doses of PCV13 by 11 months of age.[12] Reduction in penicillin-nonsusceptibility and multidrug resistance was reported concurrently in isolates from invasive disease, the middle ear, sinuses and nasopharynx in four studies.[14,15,17,18] During a randomized trial of PCV7 versus PCV13 immunization in infancy, nasopharyngeal isolates of nonsusceptible *S. pneumoniae* fell due primarily to elimination of serotype 19F after PCV7, and serotypes 6A and 19A after PCV13.[12] Because carriage determines transmission, and barring replacement serotype *S. pneumoniae* colonization with persistence, it can be expected that PCV13 will further protect against antibiotic-nonsusceptible pneumococcal infection.

If pneumococcal antibiotic nonsusceptibility continues to fall below the currently documented approximate 20%, dosage of amoxicillin orally and then parenteral therapies can be reconsidered.

Doxycycline in children under 8 years of age and dental abnormalities

Doxycycline is the only available effective treatment for rickettsial infections such as Rocky Mountain Spotted Fever (RMSF) and doxycycline is optimal therapy for *Borrelia burgdorferi* infections. Tetracyclines have carried the warning against use at <8 years because of concern for dental staining. Tetracycline binds calcium, causing discoloration of developing teeth at the time of crown calcification at 0–8 years (excluding third molars). In multiple studies since the 1950s, visible staining occurred in 23%–93% of young recipients.[19] Doxycycline binds calcium less avidly. Although no cases of staining following a 7–10 day course of doxycycline were reported, cautious avoidance was practiced. In a survey of self-reported treatment practices of healthcare providers presented with a likely case of RMSF, most correctly identified possible RMSF and 80% chose doxycycline for treatment of adolescents and adults. Only 35%, however, would prescribe doxycycline if the patient was <8 years old.[20] In a study of risk factors for fatal outcome from RMSF in a highly endemic area of Arizona, patients sought care at a median 2 days of illness. Doxycycline was begun at median day 3 in nonfatal cases, and day 7 in fatal cases.[21] Ingrained inappropriate caution against use of doxycycline in children could lead to deaths.

Investigators from the U.S. Centers for Diseases Control and the Indian Health Service accessed medical and pharmacy records of an American Indian reservation where RMSF is endemic and where exclusive healthcare of the population occurs.[19] Dental examinations using spectrophotometry for color shades were performed on 58 school-aged children who had received an average of 1.8 courses of doxycycline before 8 years of age and 213 children who never received doxycycline. Dentists unaware of subjects' doxycycline exposures detected no differences in shade of tooth color, enamel hypoplasia or staining among exposed versus unexposed subjects.

When doxycycline is indicated in children it should be prescribed regardless of the patient's age.

Azithromycin in neonates and pyloric stenosis

A macrolide antibiotic is necessary for treatment of very young infants with *Chlamydia trachomatis* infection and for treatment or prophylaxis against *Bordetella pertussis*. Erythromycin administered to approximately 200 infants at a mean 2 weeks of age because of exposure to a healthcare worker with pertussis was reported to be associated with excess cases of idiopathic hypertrophic pyloric stenosis (IHPS) in 1999.[22] The macrolide structure is a motilin-receptor agonist, stimulating migratory motor complexes in the stomach. Although there are case reports of azithromycin-associated pyloric stenosis in young infants, macrolide-associated risk incidence was unknown.

Eberly et al.[23] evaluated military health system records of infants <90 days of age born between 2001 and 2012, including 1.1 million births and approximately 1900 administered courses of erythromycin and 5000 courses of azithromycin. Approximately 2500 cases of IHPS occurred in

Table 2 Adjusted odds ratios for pyloric stenosis by age at macrolide exposure compared with age-matched unexposed infants.

Day of life at exposure	Adjusted odds ratio of idiopathic hypertrophic pyloric stenosis	
	Erythromycin	Azithromycin
1–14	13.3 (7–26)	8.3 (2.6–26)
15–42	4.1 (1.7–10)	2.9 (1.2–7)
43–90	No association	No association

Data from Eberly MD et al.[23]

macrolide *unexposed* infants (2.29 cases per 1000 population <90 days of age). Table 2 shows adjusted odds ratios for pyloric stenosis above background incidence, by drug exposure and stratified by age. Both macrolides were associated with excess cases in infants <6 weeks of age, and especially for exposure in the first 14 days of age. Of note, 80% of macrolide-associated cases occurred in males, and 30% were firstborn.

Azithromycin should be administered to neonates when indicated. The risks of pertussis and chlamydial pneumonia outweigh the risk of pyloric stenosis. Caretakers and provider should be alert for symptoms of pyloric stenosis.

Acyclovir dosing outside the neonatal period

The prospective comparative study of acyclovir doses of 60 mg/kg/day versus 40 mg/kg/day intravenously for perinatally acquired herpes simplex virus (HSV) infection confirmed acceptable safety and superiority of the higher dose for developmental outcomes at 6 months of age.[24] Differential dosing studies have not been performed in older patients. With availability of molecular diagnostics and heightened awareness of HSV as a cause of severe infection in immunocompromised children and sporadic encephalitis in otherwise healthy children, empiric acyclovir therapy is given not uncommonly, and usually to very ill patients. Some prescribers have applied the optimal dose for neonates of 60 mg/kg/day to older patients, which is inappropriate. Recommended acyclovir dose is 10—15 mg/kg/dose for HSV encephalitis in patients 3 months to 12 years, and 10 mg/kg/dose or 500 mg/m^2/dose intravenously every 8 h for a serious varicella-zoster virus infection.[25]

Investigators at Denver Children's Hospital performed a retrospective case—control study of patients treated with acyclovir intravenously who had one or more serum creatinine concentration measured after commencing therapy.[26] Renal insults were defined by reduction of estimated glomerular filtration rate (eGFR): renal risk (decrease of 25%—49%); injury (decrease of 50%—74%); and failure (decrease of ≥75%). Number of days of acyclovir therapy to the first day of worst renal dysfunction was recorded. Control groups were treated patients with repeated creatinine measurement(s) who had no renal dysfunction; cases and controls were matched by days of therapy to affected patients' "first worst" day, as well as by degree of renal insult (1:2 for renal risk, 1:4 for injury and 1:5 for failure).

Of 550 patients who received acyclovir, 373 had repeated measurement(s) of serum creatinine; 131 (35%) had a renal insult. In multivariate logistic regression analysis, acyclovir dose >15 mg/kg had odds ratio (OR) for renal risk of 3.81 (95% CI 1.55, 9.37); dose >500 mg/m^2 had OR for renal injury of 6 (95% CI 1.95, 18.47); and age >8 years or concurrent ceftriaxone had OR for renal failure of 21.5 (95% CI 2.2, >1000) and 19.3 (95% CI 1.8, >1000), respectively. Body weight >20 kg and BMI >19 kg/m^2 were highly associated with renal failure in univariate analysis but were subsumed by age >8 years and in regression analysis. Fig. 1 demonstrates in graphic form when dosage by kilograms would exceed thresholds of >500 mg/m^2 associated with nephrotoxicity.

With epidemic increases in BMI in the pediatric age group, antiviral agents such as acyclovir are more appropriately dosed by body surface area. Considering that >90% of patients treated empirically with acyclovir do not have HSV infection and are acutely ill — adding potential nephrotoxic insults of dehydration and poor perfusion, imaging studies requiring contrast enhancement, and antibiotics — it seems prudent that children beyond the age of treatment for perinatally-acquired HSV should be prescribed acyclovir not to exceed 15 mg/kg/dose *and* 500 mg/m^2/dose every 8 h.

Antibiotic stewardship to preserve health

Antibiotic stewardship to reduce emergence of severe infections due to multidrug-resistant organisms has been the focus of myriad studies and innovations. A growing number of investigations, aided by the explosion of molecular techniques to study the human microbiome, are identifying microbiologic underpinnings and population-based effects of even seemingly insignificant receipt of antibiotics in infancy on metabolism and disease later in life. Two recent cohort studies associate antibiotic

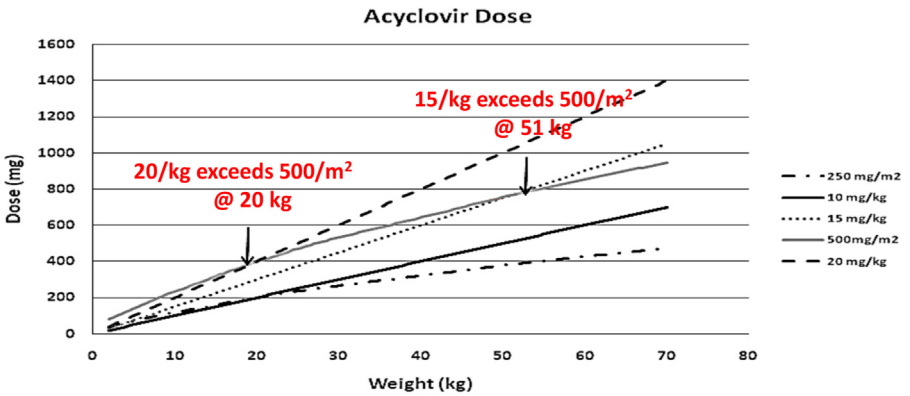

Figure 1 Comparison of acyclovir dosing by body weight and body surface area. Dosage of 20 mg/kg can be expected to exceed dosage of 500 mg/m^2 at body weight of ≥20 kg, and dosage of 15 mg/kg to exceed 500 mg/m^2 at >50 kg.

exposure in infancy with risk of being overweight in the first 24 months of life.[27,28] More prospective and powerful clarifying data undoubtedly will come. Meanwhile, a prospective family study in Utah comprised of weekly diaries of illness and weekly sampling for film array PCR testing to detect respiratory viruses over a one-year period provide powerful documentation of frequency of self-limited viral infections.[29] The study included 26 households, 108 individuals and 4166 person-weeks of study. A virus was detected in one or more family members for approximately 50% of weeks, and once per person studied approximately every four weeks. The number of children in a family was associated in a "dose-related" fashion to family detections, and a child's age <5 years with proportion of weeks the child had virus detected. Hopefully, increasing knowledge of virus infections and delineation of expected symptomatology will be a powerful disincentive to unnecessary and potentially harmful antibiotic administration for uncomplicated febrile illnesses and viral respiratory tract infections.

Conflict of interest

Dr. Long has no conflict of interest to disclose.

References

1. Lee MC, Rios AM, Aten MF, Mejias A, Cavuoti D, McCracken Jr GH, et al. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcal aureus*. *Pediatr Infect Dis J* 2004;**23**:123–7.
2. Miller LG, Daum RS, Creech CB, Young D, Downing MD, Eells SJ, et al. Clindamycin versus trimethoprim–sulfamethoxazole for uncomplicated skin infections. *N Engl J Med* 2015;**372**:1093–103.
3. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2014;**59**. e 10–52.
4. Williams DJ, Cooper WO, Kaltenbach LA, Dudley JA, Kirschke DL, Jones TF, et al. Comparative effectiveness of antibiotic treatment strategies for pediatric skin and soft- tissue infections. *Pediatrics* 2011;**128**:e479–487.
5. Fritz SA, Hogan PG, Hayek G, Eisenstein KA, Rodriguez M, Krauss M, et al. Household versus individual approaches to eradication of community-associated *Staphylococcus aureus* in children: a randomized trial. *Clin Infect Dis* 2012;**54**:743–51.
6. Fritz SA, Hogan PG, Sing LN, Thompson RM, Wallace MA, Whitney K, et al. Contamination of environmental surfaces with *Staphylococcus aureus* in households with children infected with methicillin-resistant *S. aureus*. *JAMA Pediatr* 2014;**168**:1030–8.
7. Miller LG, Eells SJ, David MZ, Ortiz N, Taylor AR, Kumar N, et al. *Staphylococcus aureus* skin infection recurrences among household members: an examination of host, behavioral, and pathogen-level predictors. *Clin Infect Dis* 2015;**60**:753–63.
8. Peltola H, Pääkkönen M. Acute osteomyelitis in children. *N Engl J Med* 2014;**370**:352–60.
9. Tetzlaff TR, McCracken Jr GH, Nelson JD. Oral antibiotic therapy for skeletal infections of children. II. Therapy of osteomyelitis and suppurative arthritis. *J Pediatr* 1978;**92**:485–90.
10. Keren R, Shah SS, Srivastava R, Rangel S, Bendel-Stenzel M, Harik N, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr* 2015;**169**:120–8.
11. Tamma PD, Milstone AM. Outpatient antibiotic therapy for acute osteomyelitis in children: balancing safety and efficacy. *JAMA Pediatr* 2015;**169**:108–9.
12. Dagan R, Juergens C, Trammel J, Patterson S, Greenberg D, Givon-Lavi N, et al. Efficacy of 13-valent pneumococcal conjugate vaccine (PCV13) versus that of 7-valent PCV (PCV7) against nasopharyngeal colonization of antibiotic-nonsusceptible *Streptococcus pneumoniae*. *J Infect Dis* 2015;**211**:1144–52.
13. Camacho-Badilla K, Falleiros-Arlant LH, Brea J, Avila-Aguero ML. Challenges in the surveillance of invasive pneumococcal disease in the postvaccination era. *J Pediatr Infect Dis Soc* 2015;**4**:91–3.
14. Kaplan SL, Center KJ, Barson WJ, Ling-Lin P, Romero JR, Bradley JS, et al. Multicenter surveillance of *Streptococcus pneumoniae* isolates from middle ear and mastoid cultures in the 13-valent pneumococcal conjugate vaccine era. *Clin Infect Dis* 2015;**60**:1339–44.
15. Lindstrand A, Bennet R, Galanis I, Blennow M, Ask LS, Hultman S, et al. Sinusitis and pneumonia hospitalization after introduction of pneumococcal conjugate vaccine. *Pediatrics* 2014;**134**:e1528–1536.
16. Ben-Shimol S, Givon-Lavi N, Leibovitz E, Raiz S, Greenberg D, Dagan R. Near- elimination of otitis media caused by 13-valent pneumococcal conjugate vaccine (PCV) serotypes in southern Israel shortly after sequential introduction of 7-valent/13-valent PCV. *Clin Infect Dis* 2014;**59**:1724–32.
17. Ben-Shimol S, Greenberg D, Hazan G, Givon-Lavi N, Gottesman G, Grisaru-Soen G, et al. Differential impact of pneumococcal conjugate vaccines on bacteremic pneumonia versus other invasive pneumococcal disease. *Pediatr Infect Dis J* 2015;**34**:409–16.
18. Tam P-Y, Madoff LC, Coombes B, Pelton SI. Invasive pneumococcal disease after implementation of 13-valent conjugate vaccine. *Pediatrics* 2014;**134**:210–7.
19. Todd SR, Dahlgren FS, Traeger MS, Beltrán-Aguilar ED, Marianos DW, Hamilton C, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. *J Pediatr* 2015;**166**:1246–51.
20. Zientek J, Dahlgren FS, McQuiston JH, Regan J. Self-reported treatment practices by healthcare providers could lead to death from Rocky Mountain spotted fever. *J Pediatr* 2014;**164**:416–8.
21. Regan JJ, Traeger MS, Humphreys D, Mahoney DL, Martinez M, Emerson GL, et al. Risk factors for fatal outcome from Rocky Mountain spotted fever in a highly endemic area — Arizona, 2002–2011. *Clin Infect Dis* 2015;**60**:1659–66.
22. Centers for Disease Control and Prevention. Hypertrophic pyloric stenosis in infants following pertussis prophylaxis with erythromycin — Knoxville, Tennessee, 1999. *Morb Mortal Wkly Rep* 1999;**48**:1117–20.
23. Eberly MD, Eide MB, Thompson JL, Nylund CM. Azithromycin in early infancy and pyloric stenosis. *Pediatrics* 2015;**135**:483–8.
24. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001;**108**:230–8. PMID: 11483782.
25. American Academy of Pediatrics. Non-HIV antiviral therapy. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. *Red book 2015 report of the committee on infectious diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015. p. 919.
26. Rao S, Abzug MJ, Carosone-Link P, Peterson T, Child J, Siparsky G, et al. Intravenous acyclovir and renal dysfunction

in children: a matched case control study. *J Pediatr* 2015;**166**:1462—8.
27. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr* 2014;**168**:1063—9.
28. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. *Pediatrics* 2015;**135**:617—26.
29. Byington CL, Ampofo K, Stockmann C, Adler FR, Herbener A, Miller T, et al. Community surveillance of respiratory viruses among families in the Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) study. *Clin Infect Dis* 2015;**61**:1217—24.