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Optimizing antimicrobial therapy in children

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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

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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