Current concepts in the management of bacterial skin infections in children

Aparna Palit, Arun C. Inamadar

Department of Dermatology, Venereology and Leprosy, SBMP Medical College, Hospital and Research Center, BLDE University, Bijapur - 586 103, Karnataka, India

Address for correspondence:
Dr. Arun C. Inamadar, Professor and Head, Department of Dermatology, Venereology and Leprosy, SBMP Medical College, Hospital and Research Center, BLDE University, Bijapur – 586 103, Karnataka, India. E-mail: aruninamadar@rediffmail.com

ABSTRACT

Bacterial skin infections in children vary widely clinically, starting from mild superficial folliculitis to deep necrotizing fasciitis. The causative organisms are mostly *Staphylococcus aureus* and *Streptococcus*, with occasional involvement of Gram-negative organisms. Treatment of even the milder forms of bacterial skin infections is of importance because of the long-term morbidity associated with them. However, because of global emergence of resistant strains of bacteria, treatment of these conditions is becoming increasingly difficult. The current antibacterial resistance patterns in organisms causing skin and soft tissue infections and the problems encountered in their management in children have been discussed.

Key words: Bacterial infections, children, skin, cellulitis, impetigo, methicillin-resistant *S. aureus*, methicillin-sensitive *S. aureus*,

INTRODUCTION

Bacterial skin infections are one of the most common infections encountered in the pediatric age group, especially in the developing world. These include 'primary bacterial infections' and 'secondary bacterial infections' superimposed on other dermatoses and traumatic or post-surgical wounds. Recurrent pyoderma is a problematic infection experienced by children with or without underlying dermatological disorders or immunodeficient states.

Majority of skin infections are caused by Gram-positive bacteria, most commonly *Staphylococcus aureus* and group A β-hemolytic *Streptococcus* (GABHS).[1,2] Some Gram-negative organisms and anaerobes may also cause pyogenic skin infections. With rapidly increasing resistance to antibacterial agents, management of bacterial infections is becoming increasingly difficult. Other organisms like *Mycobacteria* sp. and *Treponema pallidum* may also cause childhood cutaneous infections but are beyond the scope of this discussion.

BACTERIAL SKIN INFECTIONS IN CHILDREN

Types

Skin and soft tissue infections (SSTIs) can be classified as 'superficial' (epidermis and dermis) and 'deep' (hypodermis, fascia and muscle).[3] According to the setup from where the infection is contacted, it may be 'community acquired' (CA) or 'hospital acquired/ nosocomial' (HA) infection. The former usually involves a single pathogen, whereas the latter is often polymicrobial. Different clinical types of bacterial infections in children are listed in Table 1.

SSTIs are considered '*complicated*'[4]

- When deeper structures like fascia and muscle are involved, necessitating surgical intervention;
- When the child has associated co-morbidity like diabetes mellitus or other immunosuppressed states, affecting the response to usual treatment;
- When they involve the perineal and/ or perianal region, with the risk of infection by anaerobic and Gram-negative pathogens.

Table 1: Bacterial skin and soft tissue infections with common causative organisms[1,3,7,31]

Types	Organism	Predisposing factors/Complications
SUPERFICIAL INFECTIONS:		

Impetigo
  Bullous
  Non-bullous
	
	S. aureus
	S. aureus, GABHS
		Bullous impetigo: SSSS.
		Non-bullous impetigo: Precipitating factors:
		trauma, insect bite, varicella, scabies.
		Involvement of 'dangerous area of face'; risk of
		cavernous sinus thrombosis.

Folliculitis, furuncle, carbuncle	*S. aureus*	Folliculitis: recurrence. Furuncle, carbuncle: If untreated, necrotizing fasciitis may develop.
Cellulitis	GABHS, other Streptococci, *S. aureus* Buccal cellulitis in infants: *H. influenzae* Perianal cellulitis in children: GABHS	Common in children with diabetes/ immunosuppression. Buccal cellulitis in the presence of otitis media.
Erysipelas	GABHS, *S. aureus*	
Surgical and traumatic wound infection	Polymicrobial	
Neonatal mastitis and scalp abscesses	*S. aureus,* GABHS, Gr B and D Streptococci, anaerobes, Enterococci	Scalp abscesses may be secondary to scalp electrode application, used for fetal heart rate monitoring. Mastitis/ breast abscess is commoner in full-term infants.
Neonatal omphalitis	*S. aureus, E. coli, Klebsiella* sp*.,* Gr B *Streptococci*	Home delivery and unhygienic cord care are the predisposing factors. May progress to life-threatening fasciitis if not recognized early. Other complications are intra-abdominal abscess and evisceration of small bowel.
Periorbital cellulitis	*S. pneumoniae, H. influenzae, S. aureus*, GABHS, anaerobes	Sinusitis is a major predisposing factor.
Animal bite wounds Human bite wounds	Polymicrobial *Pasteurella multocida* *S. aureus* *Streptococcus* sp. *Campnocytophaga canimorsus* *S. aureus, Eikenella corrodens*, oral anaerobes, *Peptostreptococcus*, *Bacteroides*	Cat-bite inflicts deep puncture wounds, inoculating microorganisms at deeper tissues, with higher risk of infection.
DEEPER INFECTIONS:		
Orbital cellulitis	*S. pneumoniae, H. influenzae, S. aureus*, GABHS, anaerobes	Sinusitis is a major predisposing factor. Risk of cavernous sinus thrombosis
Necrotizing fasciitis	GABHS, often polymicrobial in post-surgical cases, including other Gram+, Gram− organisms and anaerobes, *Vibrio vulnificus, Aeromonas hydrophilia*	Childhood varicella and the use of NSAIDs following it, are the risk factors. Toxic appearance, thrombocytopenia Medical and surgical emergency.
Pyomyositis (Skeletal muscle abscess)	*S. aureus*, GABHS, *Clostridium perfringens*	Affects children mainly in the tropical countries.
Post-surgical wound infection	Polymicrobial, *S. aureus,* enteric pathogens and anaerobes	
TOXIN-MEDIATED INFECTIONS:		
Staphylococcal scalded skin syndrome (SSSS)	*S. aureus* (exfoliative toxins ETA, ETB, ETD)	Premature neonates are at risk to develop SSSS because of improper renal excretion of the exfoliative toxins. Super-added infection of denuded skin in neonates and small children by Gram-negative organisms.
Toxic shock syndrome (TSS)	*S. aureus* (TSS-1 toxin, enterotoxin) *Streptococcus* (pyrogenic and mitogenic toxins)	Risk factors for staphylococcal TSS: post-surgical patients, AIDS, URTI, influenza and parainfluenza. Risk factors for streptococcal TSS: invasive streptococcal infection.

EPIDEMIOLOGY

Bacterial skin infections are one of the most common causes of childhood morbidity and constitute one of the prime causes of hospital attendance in children. In an epidemiological study of skin diseases among school children in north India, incidence of bacterial pyoderma (impetigo, folliculitis and infected bite reactions) was found to be 64.4% among all skin infections, compared to 13.4% among the controls.[5] In another retrospective study of skin disorders among children (<12 years of age) conducted at New Delhi, bacterial infections were recorded among 58.09% of the children.[6]

S. aureus is the commonest pathogen present in more than 70% of cases of all SSTIs[1] and in approximately 50% of cases of cellulitis.[7] In a community-based Indian study, of the 250 cases of pyoderma at all ages, *S. aureus* was isolated in 80.8% of cases.[8]

Methicillin-resistant *S. aureus* (MRSA) was recognized initially in the health-care setup (1960s), followed by its spread in the community (1980s).[9] The incidence of MRSA is variable (1%-74%) in geographic areas and among various communities in different countries.[10-12] Currently, community-acquired MRSA (CA-MRSA) has emerged as the most commonly identified pathogen in SSTIs in many areas[13] and accounts for >90% of SSTIs in children.[14] Outbreaks of CA-MRSA SSTIs are known to occur in child care centers and newborn nurseries.[15]

In a study conducted amongst patients of all ages in south India, suffering from bacterial skin infections, the incidence of MRSA was found to be 10.9%.[8] In another hospital-based prospective study conducted among children in north India (2004), the incidence of CA-MRSA was found to be 6.9%,[16] indicating a lower prevalence of the organism in that region of the country during the study period. Even in the endemic regions, most SSTIs are treated without culture of infective material, which impairs the detection of correct prevalence of CA-MRSA in the community.[13]

MICROBIAL ORGANISMS

Practically, *S. aureus* is the major pathogenic organism for SSTIs, followed by *Streptococcus* in some cases. Others include *Streptococcus agalactiae* and group C and G streptococci.[2] Rarely, Gram-negative pathogens like *Pseudomonas aeruginosa*, *Klebsiella* sp., *Escherichia coli* and anaerobes are involved.

In SSTIs caused by *S. aureus,* the prime factor to be considered is in distinguishing between MRSA (community and hospital acquired) and methicillin-sensitive *S. aureus* (MSSA). The clinical spectrum of the disease caused by CA-MRSA (most frequently furuncles, carbuncles and abscesses) is similar to that of MSSA.[9] Clinical and epidemiological characteristics may not be helpful in distinguishing these two variants.[17]

However, possible clinical indicators of MRSA infections are as follows:
- Evidence of concomitant lung (associated cough) and skin infection
- Presence of localized peri-umbilical folliculitis
- Excessive pain, beyond clinician's expectation

Post-hospitalization outcome of the patients with SSTIs caused by either of these two strains remains similar.[18] Moreover, high rate of antibacterial resistance has been observed in both.[19] However, CA-MRSA is more likely to cause SSTIs (70%-90% of all staphylococcal infections) as compared to MSSA, and spread to close contacts is commoner with the former.[3]

The practical purpose of distinguishing between MSSA and MRSA is the fact that the latter is not sensitive to anti-staphylococcal penicillins and cephalosporins, which are used as first-line anti-staphylococcal therapy.[2]

MANAGEMENT

Majority of the superficial bacterial infections can be managed on an outpatient basis (outpatient management). The decision of inpatient management (hospitalized management) depends on the following factors[3]:
- Depth and extent of the infection
- Unusual clinical presentation
- Presence of complications/ risk factors
- Systemic involvement
- Underlying immunosuppressed state

Occasionally, superficial infections like erysipelas and cellulitis may necessitate hospitalization if signs of rapid progression develop.

ISSUES IN THE MANAGEMENT OF BACTERIAL INFECTIONS

1. Antibacterial resistance
Systemic drugs
In children, majority of the SSTIs are caused by either *S. aureus* or GABHS or a combination of both. In various institutions in India, empiric treatment for SSTIs is the norm rather than specific antibacterial treatment following culture and sensitivity test. Hence awareness about regional pattern of antibiotic sensitivity/ resistance of the prevalent microorganisms is of immense importance.

Emerging antibacterial resistance of *S. aureus* is the main issue in the management of bacterial skin infections in children. Penicillin-resistant (β-lactamase–producing) strains of *S. aureus* predominate the nosocomial infections, and currently only <5% of the *S. aureus* strains are penicillin-sensitive.[3] MRSA is on the rise in SSTIs in children both in the hospital setup (HA-MRSA) and in the community. Methicillin resistance is acquired through *mecA* gene carried in staphylococcal cassette chromosome (SCCmec).[3] It has been observed that as compared to CA-MRSA, HA-MRSA strains are frequently resistant to multiple antibacterials, and this is conferred to SCCmec type IV, present in the former.[3] SCCmec types IV and V, because of their smaller size, allow easy horizontal spread of the resistance among community strains.[3,14]

In the hospital setup, coagulase-negative staphylococci (CoNS) have become a pathogen of concern. These are methicillin-resistant in 50% of cases and also show resistance to macrolides, clindamycin and co-trimoxazole.[20]

Erythromycin resistance has been found to vary from 3% to 74% in *S. aureus*[12] and more so in *S. pyogenes* in different studies from across the world, which makes it unsuitable for empirical treatment of SSTIs in children.[21] In a community-based study of pyoderma from India, prevalence of erythromycin-resistant strains of *S. aureus* was found to be 56.4%.[8]

Both *S. aureus* and streptococci may show resistance to MLS agents (macrolide, lincosamide, streptogramin B), which is mediated by methylation of 23SrRNA, inhibiting effective ribosomal binding of the antibacterials.[4] If such resistance is constitutive,

resistance to all the three MLS group of antibacterials is present; whereas if it is inducible, resistance is mostly only to macrolides.[4] Clindamycin is currently considered as the empirical treatment of choice for CA-MRSA; but erythromycin-resistant MRSA strains also show inducible clindamycin resistance, and in these cases, treatment failure with clindamycin is common.[1,3] Reported clindamycin resistance rates in pediatric HA-MRSA are 27% to 44%, and those of co-trimoxazole are 0% to 11%.[22,23]

Vancomycin is a drug of choice for nosocomial MRSA. However, there is emergence of vancomycin-resistant strains of *S. aureus* (VRSA) and enterococci following its expanded use.[2,3] Some strains show intermediate-level resistance, designated as vancomycin-intermediate *S. aureus* (VISA).[1] Some strains of *S. aureus* show hetero-resistance (hVISA) to vancomycin.[15] Vancomycin-resistant enterococci (VRE) in the hospital setup remain a therapeutic challenge.[2] Factors promoting emergence of VRE include the following[2]:
- Prolonged hospital/ intensive care unit stay
- Recent surgery, renal failure
- Immunosuppression and post organ transplantation
- Close proximity to a hospitalized patient with VRE colonization

Linezolid is an effective antibiotic in treating VRE infection, but resistance has been reported. Pediatric cases of linezolid-resistant MRSA infection have been reported, associated with prolonged low-dose therapy.[24]

Several Gram-negative pathogens (*E. coli, Klebsiella* sp.) produce extended-spectrum β-lactamase (ESBL),[2] conferring resistance to commonly used drugs. *P. aeruginosa* shows resistance to aminoglycosides and *E. coli* to earlier generation of fluoroquinolones, piperacillin and ticarcillin.[25]

Over-the-counter availability of antibiotics in India and their indiscriminate use facilitates development of resistance. In a prospective study conducted among children with pyoderma in north India (2004), the incidence of multi-drug resistance was recorded to be 16.8%.[16] Among the strains of *S. aureus* isolated in this study, resistance to common antimicrobial agents was high; 90.6% for penicillins, 39.4% for co-trimoxazole and 23.2% for erythromycin.[16]

Topical drugs

Staphylococci show resistance to all commonly used topical agents with anti-staphylococcal activity, e.g., mupirocin- 2%, fusidic acid- 2% and silver sulfadiazine- 1%.[26] Fusidic acid and mupirocin resistances are of growing concern in many countries.

Mupirocin resistance has been reported to be as high as in 50% of the isolates,[27] and this is more so in infections with CA-MRSA.[26] There are reports of gradually increasing resistance to fusidic acid (fusidic acid–resistant *S. aureus*), which has been attributed to over-usage as well as to monotherapy.[28,29] Even clinical isolates of *S. epidermidis* have been reported to show high prevalence of fusidic acid resistance.[30] Cross resistance to fusidic acid may be present in some of the CA-MRSA isolates with mupirocin resistance.[26]

2. Virulence factor of organisms

Some of the CA-MRSA clones are more virulent and are transmitted more effectively through communities over widespread geographic areas,[11,30] causing difficulties in the management. Some CA-MRSAs have Panton-Valentine-Leukocidin (PVL) genotype, which contributes to severe, necrotizing skin infections.[13]

3. Immunocompromised children

Immunocompromised states related to primary immunodeficiency disorders or those secondary to malignant diseases or immunosuppressive therapy pose special problem in the management of SSTIs in children. Neutropenia is common in children on cancer chemotherapy, and such children are at special risk of developing infection (cellulitis/ ecthyma gangrenosum) by Gram-negative organisms like *P. aeruginosa*.[1] HIV-infected children are at higher risk of developing both CA-MRSA and HA-MRSA SSTIs, and are associated with increased mortality.[3]

Infection is usually polymicrobial in immunocompromised children, common organisms being *S. aureus* and *P. aeruginosa,* which require broad-spectrum antimicrobial coverage.

Children with risk factors for developing HA-MRSA infection are more likely to develop invasive disease.[15]

4. Recurrent infections

Recurrence is common in milder forms of SSTIs (folliculitis, abscess, impetigo, etc.), and management of such cases is challenging for the physicians. Recurrent skin abscess caused by MRSA is a common problem and may be related to the fact, that the organism causes environmental contamination and so eradication is difficult.[15]

Recurrence may result from the following causes:
- Inadequate treatment or inappropriate choice of antibiotics
- Underlying skin disease which was left uncared for during treatment of infections, e.g., scabies, atopic dermatitis, tinea capitis, contact dermatitis and psoriasis
- Colonization with drug-resistant strains of bacteria; there is an increased incidence of skin colonization with CA-MRSA in children[3]
- Underlying immunosuppression

5. Non-availability and non-affordability of drugs

Many of the newer classes of antibacterials are not freely available in different parts of India and even if available are not affordable by people from low socioeconomic strata, who are the common sufferers of SSTIs.

GENERAL MEASURES IN THE MANAGEMENT OF SSTIs IN CHILDREN[3]

Following aspects should be taken care of in children with SSTIs:
- Careful elicitation of history and detailed clinical examination.
- Drainage of pus or debridement of necrotic tissue as required; as per current guidelines for management of SSTIs, incision and drainage of fluctuant lesions is recommended.[31] In one of the Indian studies in children with pyoderma, incision and drainage of the lesions was not required for any of the patients, and this did not alter the outcome of antibiotic therapy.[16] However, incision and drainage of fluctuant lesions, in addition to other advantages, brings symptomatic relief to the patient. Warm compress should be continued to facilitate drainage.
- Assessment of the immune status of children with recurrent SSTIs by careful history and necessary ancillary investigations.
- Identification of symptoms and signs of systemic spread, e.g., fever may be indicative of bacteremia or secondary organ involvement. Neonatal SSTIs with persistent fever may require a lumbar puncture (to rule out meningitis) and chest X-Ray (to rule out pneumonia).[3]

- Adequate treatment of underlying skin disorders like scabies or atopic dermatitis.
- Traumatic wounds and bite wounds require prophylaxis for tetanus and rabies. In animal bites, immediate wound cleaning with splashes of water is of vital importance. Decision on wound closure is guided by its site and time lapse since the infliction of injury. Debridement of necrotic tissue and delayed wound closure are considered in some cases.[1,3]

ANTIBACTERIAL THERAPY

SSTIs occurring in children either in community or hospital setup cause significant morbidity and warrant judicious antibacterial therapy.

Choice of antibacterial agents should ideally be guided by bacterial culture sensitivity tests from the infective material collected from the site of infection (e.g., pus, aspirated fluid). In children, it may be difficult to undertake invasive procedures like aspiration, and in such situations surface swab of the infected site may be attempted. However, culture results from such specimens are often misleading.[4] Since culture sensitivity results are available at an approximate interval of 72 hours, empirical antibacterial therapy can be started, followed by streamlining of antibiotic therapy once the reports are in hand. Empiric therapy should also be considered in places where culture sensitivity test is not easily accessible.

The choice of empirical antibacterial therapy should be guided by[2]:
- Factors like whether the infection is community acquired/ nosocomial and uncomplicated/ complicated.
- Existing knowledge of prevalent pathogens and the antimicrobial sensitivity pattern in that region.
- Clinical features of the patient; certain clinical features are pointers to the causative organism. Cellulitis caused by *S. aureus* tends to be localized, with local abscess formation; whereas streptococcal cellulitis is more diffuse, rapidly spreading and associated with lymphangitis.[3]
- Clinician's experience in treating SSTIs.

Basic principles in the choice of empirical antibacterial therapy
Systemic therapy
In children, majority of the SSTIs are caused by *S. aureus* or GABHS, and the choice of antibiotics should

aim at targeting these organisms. In the era of multi-drug resistance, there are several newer antibiotics in the armamentarium of the treating clinicians [Table 2].

Penicillinase-resistant penicillins (cloxacillin, dicloxacillin, flucloxacillin, methicillin, nafcillin) remain the treatment of choice for MSSA, as these show consistent effectiveness in such infections, are cheaper and have minimal adverse effects. Combinations of penicillinase-sensitive penicillins with penicillinase inhibitors (e.g., amoxicillin+clavulanic acid, ticarcillin+clavulanic acid, piperacillin+tazobactum) are the newer group of drugs for treating MSSA.[3] Use of these agents provides protection against Gram-negative organisms also, and these are useful for polymicrobial infections. Ampicillin+sulbactum is a well-tolerated drug in children.[32]

Cephalosporins are effective against *S. aureus, S. pyogenes* and many Gram-negative organisms. First generation cephalosporins have more frequent dosage schedules (4-6 hourly), except cefadroxil (12 hourly), and hence are less favored. In general, these groups of drugs are well tolerated by children because of good taste and fewer side effects. Cefuroxime axetil, a prodrug, can be used both orally (uncomplicated SSTIs) and parenterally (severe SSTIs) in children. Several third generation cephalosporins show good effect against both Gram positive and Gram negative organisms and are often used for SSTIs. Cefixime is not effective against *S. aureus* as it has low affinity for β-lactam binding proteins.[3] Ceftriaxone may be used in moderate to severe pediatric SSTIs, even on outpatient basis, because of its convenient once-daily dosage schedule.[3]

Co-trimoxazole is a suitable drug for the treatment of staphylococcal infections in children;[33] however, some authors found it to be ineffective for this purpose.[13,34] Co-trimoxazole is not active against GABHS and should not be used as monotherapy in SSTIs caused by this organism.[13] Failure in many cases of co-trimoxazole therapy in non-cultured SSTIs may be attributed to this cause.[13] However, it is a drug that Indian clinicians are experienced with and is easily available at all levels of health-care facilities.

Mild to moderate skin infections can be treated with erythromycin, but it is unsuitable for severe infections because of its bacteriostatic property.[35] In regions

Class	Compound	Mechanism of action	Comment
SYSTEMIC			
Cephalosporins	*2nd generation* Cefprozil Cefuroxime axetil Loracarbef *3rd generation* Cefpodoxime proxetil Cefdinir Cefditoren pivoxil	Inhibits bacterial cell wall synthesis.	Effective with broader spectrum of activity but no added benefit and significantly more expensive. Loracarbef has enhanced stability against some β-lactamases and better tolerability, but expensive.
Carbapenem	Meropenem Ertapenem	Inhibits bacterial cell wall synthesis by binding penicillin-binding proteins.	Potent against Gram+, Gram− and ESBL-producing organisms.
Macrolides	Clarithromycin Azithromycin Dirithromycin Roxithromycin	Inhibition of RNA-dependent protein synthesis by binding to 50S subunit of 70S ribosome.	
Fluoroquinolones	Levofloxacin Gatifloxacin Moxifloxacin	Inhibition of bacterial DNA gyrase.	Improved oral bioavailability and longer serum elimination half lives. Moxifloxacin: US-FDA approved for T/T of uncomplicated SSTIs in adults.
Oxazolidinones	Linezolid	Acts at pretranslational focus to prevent bacterial protein synthesis by inhibiting formation of 70S-initiation complex.	US-FDA approved for T/T of uncomplicated SSTIs caused by MSSA/ *S. pyogenes* and complicated SSTIs caused by MRSA and *Streptococcus* sp.
Streptogramins	Quinupristin/ Dalfopristin (30:70, w/w molar ratio)	Act sequentially; dalfopristin interferes with peptidyl transferase on 50S ribosome, while quinupristin inhibits peptide chain elongation of 50S ribosome. Synergistic action.	Bactericidal against Gram+ bacteria, bacteriostatic for VRE and MRSA. US-FDA approved for T/T of complicated SSTIs caused by MSSA and *S. pyogenes.*
Cyclic lipopeptide	Daptomycin	Ca++ dependent disruption of bacterial membrane ionic electric potential and inhibition of macromolecular synthesis.	Rapidly bactericidal. US-FDA approved for T/T of complicated SSTIs.
Glycopeptides	Dalbavancin Oritavancin	Inhibits biosynthesis of peptidoglycans.	High protein binding giving very long half lives; once daily to once weekly dosage. Useful in presence of vancomycin-resistant staphylococcal infections.
Glycyclines	Tigecycline	Binds to the bacterial 30S ribosome, blocking entry of transfer RNA. This prevents protein synthesis by halting the incorporation of amino acids into peptide chains and thus limits bacterial growth.	Tetracycline group of drug, structurally related to minocycline. Activity against a broad spectrum of microorganisms, including MRSA and MSSA. Indicated in treatment of adults with complicated SSTIs.
TOPICAL			
Pleuromutilin	Retapamulin	Inhibits bacterial protein synthesis by selective binding to ribosomes.	Mainly bacteriostatic for *S. aureus* and *S. pyogenes.* Approved for treatment of uncomplicated SSTIs caused by *S. aureus* (excluding MRSA) and *S. pyogenes* and infected minor wounds in patients at and above 9 months of age. Shows *in vitro* post-antibiotic residual effect, suggesting effectiveness even in case of poor compliance.
Indolmycin		Targets enzyme tryptophanyl-tRNA synthetase.	

with lower resistance to erythromycin, it is a cheap and effective alternative to penicillinase resistant penicillins in treating childhood pyoderma. It is an alternative drug for children allergic to penicillin or co-trimoxazole. The newer macrolides have wider antibacterial spectrum of action, and these are

concentrated in neutrophils with phagocytosed *S. aureus,* ensuring more effective killing.

In a systematic review of 26 studies related to pediatric SSTIs, treatment failure related to MRSA infection was not quoted.[34] CA-MRSA infections are usually nonresponsive to β-lactams alone, and these can be treated initially with co-trimoxazole (98%-100% sensitivity) or clindamycin (95%-98% sensitivity).[35] While choosing clindamycin, due care should be taken to identify 'inducible' and 'constitutive clindamycin resistance,' though, practically, this is not associated with significant treatment failure.[14] Clindamycin is bacteriostatic, and its liquid preparation is extremely unpalatable, making it difficult to use in children.[13] There is rare possibility of a fatal complication, pseudomembranous colitis, with use of clindamycin.[3]

For severe SSTIs due to MRSA, intravenous vancomycin is the antibacterial of choice. Otherwise, this antibiotic is less effective than β-lactams against *S. aureus,* and indiscriminate use is associated with the risk of development of VRE. Hence its use must be restricted to severe MRSA infection or other multi drug resistant Gram-positive bacterial infections. Teicoplanin has the advantages of antibacterial spectrum that is identical to that of vancomycin, more potency, particularly against *Streptococcus* sp. and *Enterococcus* sp.*;* single daily dosage schedule; fewer side effects; and option for change to oral route following intravenous therapy. Pediatric use of teicoplanin has been limited to children on cancer chemotherapy.

Linezolid is effective against MSSA, MRSA, VISA, *S. pyogenes,* VRE and many anaerobes. Against staphylococci and enterococci, linezolid is bacteriostatic, but is bactericidal for streptococci.[2] It is highly effective for the treatment of SSTIs due to MRSA in children (>90% cure rates, comparable to IV vancomycin),[15] but its use should be restricted only for treatment of multi drug resistant organisms. Though well tolerated in children, serious side effects may occur and the higher cost may limit its use. However, it is a cheaper alternative to vancomycin.

Streptogramins (Quinupristine/ Dalfopristine) have antibacterial spectrum that is similar to that of linezolid, but experience of using this drug in pediatric population is limited. Mostly these drugs have been used in hospitalized children with underlying immunosuppression.

Fluoroquinolones have broad spectrum activity against both Gram positive and Gram negative organisms but are not licensed for use in children.

Topical therapy

Indications for monotherapy with topical antibiotics are as follows:
- Localized lesions
- Absence of regional lymphadenopathy
- Absence of systemic features
- The child is otherwise healthy (no underlying cutaneous/ systemic disorders)

The optimal dosage schedules of commonly used topical antibiotics, viz., mupirocin 2% ointment/ cream and fusidic acid 2% cream, for treatment of localized pyoderma are up to 3 times daily for up to 10 days.[36]

Efficacy of these two agents in treating primary and secondary pyoderma has been found to be comparable in different studies.[37] However, as compared to mupirocin, topical fusidic acid is 40% to 80% more cost effective.[37]

Though there are increasing reports of mupirocin resistance, practically it seems to be much lower.[26] Topical mupirocin has been proved to be as effective as oral erythromycin in uncomplicated impetigo in children.[38] Efficacy of mupirocin is impaired in the presence of serum and also in weeping lesions because of high protein binding.[39]

In many European countries, monotherapy with topical fusidic acid is not preferred currently, in view of the widespread resistance shown by both MSSA and MRSA; and combination of this topical agent with systemic oxazolidinones has been suggested.[29]

Other agents that are active against MRSA are silver sulphadiazine, newer topical agents like retapamulin and indolmycin.[26]

Topical application of retapamulin 1% ointment twice daily for 5 days was found to be as effective as fusidic acid and well tolerated by children.[40] This newer topical drug is an effective alternative in infections with mupirocin-resistant and fusidic acid–resistant

strains of *S. aureus*,[41] and its efficacy is comparable to oral cephalexin.[40] Topical indolmycin is active against fusidic acid–resistant and mupirocin-resistant MRSA and also shows *in vitro* activity against MSSA and VISA.[26] Topical gentian violet 1% shows anti-MRSA activity, but use of this agent is messy and gives an unsightly appearance.

ROLE OF COMBINATION ANTIBIOTIC THERAPY

In the treatment of SSTIs due to MRSA, intravenous clindamycin may be used as an adjunct to vancomycin. Many other antibiotics are effective in MRSA infections but do not yield desirable results when used alone, either because their anti-staphylococcal activity is lower or there is development of resistance while the patient is on therapy. These drugs include rifampicin, trimethoprim, fusidic acid, aminoglycosides and fosfomycin.[3] If these drugs are used, combination therapy is preferred in order to prevent development of resistance.[3,15] Choice of combination should be guided by local resistance pattern of the bacteria and drug sensitivity of the MRSA isolate. Experience of using these drugs in treating childhood SSTIs is limited.

In an Indian study of bacterial pyoderma in children, majority of the patients were treated effectively with oral cloxacillin and cephalexin.[16] The other drugs used were co-trimoxazole, erythromycin and ampicillin. Three cases of CA-MRSA, recorded by the authors, were treated effectively with oral linezolid, lincomycin and topical mupirocin. In the authors' experience, co-trimoxazole therapy was associated with slow response or recurrence.[16]

Among the newer antibiotics, except streptogramins, data regarding usage in children are not available.[15] Streptogramins are not yet approved for use in children younger than 16 years of age.[15] These drugs are to be reserved for severe, complicated SSTIs with resistant pathogen.

To summarize,[1-3]
* Mild, localized pyoderma (e.g., folliculitis, impetigo), in the absence of systemic features (e.g., fever, lymphadenopathy) and any risk factor, can be treated with a course of topical antibiotic (e.g., mupirocin) for 7 to 10 days. In case of inadequate response or development of complications, switch over to oral systemic therapy is recommended.

* In other community-acquired SSTIs, oral anti-staphylococcal penicillin, e.g., nafcillin or oxacillin or cefazolin, remains the first line drug for empiric therapy;
* Otherwise healthy children with CA-MRSA infection may be treated with oral clindamycin or co-trimoxazole.[3]
* Clindamycin and linezolid are the only two options for oral monotherapy in infections with MRSA, MSSA and GABHS.[13]

The above treatment protocols can be followed on outpatient basis. However, option of hospitalization should be kept open if these treatment modalities are ineffective, causing significant disease progression/ complication.
* In severe suspected infection with CA-MRSA or HA-MRSA, parenteral vancomycin/ teicoplanin are the first-line therapy, followed by switch over to oral linezolid.
* In hospital-acquired SSTIs, piperacillin + tazobactum, with or without vancomycin/ teicoplanin, is to be used.
* Nosocomial Gram negative pathogens (mostly *P. aeruginosa*) can be treated with piperacillin + tazobactum. Carbapenems remain the drug of choice for ESBL producing Gram-negative organisms.[2]
* In penicillin-allergic patients, treatment options include macrolides, clindamycin or cefazolin; third generation cephalosporin like ceftazidime and aminoglycosides; vancomycin; or linezolid — depending upon the severity of infections and the presence of risk factors.

Empirical treatment regimens for some of the specific clinical types of SSTIs have been presented in Table 3.

TREATMENT OF COLONIZATION

Anterior nares (30%-70%), axillae and perineum are the classical sites of colonization by *S. aureus*.[14] In neonates, in addition to the above sites, periorbital region, umbilical stump and peri-umbilical region are colonized.

Anterior nares is the primary site for colonization of MRSA, and such colonization is not necessarily associated with active infection.[9] However, various study results have shown that people colonized with *S. aureus* carry a greater chance of subsequent infection

Table 3: Empiric treatment for some skin and soft tissue infections[1-3]

Skin and soft tissue infections	Antibiotics	Dosage in children	Duration of treatment
Erysipelas	Benzyl penicillin/ Clindamycin/ Cefazolin	Benzyl penicillin 100,000-400,000 units/kg IV/ IM 4-6 hourly. Clindamycin 15-40 mg/kg (max. 4-8 g) IV 6-8 hourly. Cefazolin 25-150 mg/kg IV/ IM 8 hourly	7-10 days
Cellulitis	Cefazolin/ Clindamycin Linezolid in MRSA	Dose as above for other drugs Linezolid 10 mg/kg/d 12 hourly.	7-14 days
Bullous/ non-bullous impetigo	Few localized lesions: topical mupirocin. Widespread lesions/ risk factors: systemic Cloxacillin/ Cefazolin	Cloxacillin 100-200 mg/kg (max. 12 g) IV 4-6 hourly. Dicloxacillin 25 mg/kg/d 6 hourly. Dose as above for other drugs	7-10 days
Folliculitis, furuncle, carbuncle	Few localized lesions: topical mupirocin. Widespread lesions/ risk factors: systemic benzyl penicillin/ Cefazolin/ Clindamycin	Dose as above for systemic agents	7-10 days
Periorbital cellulitis	Cefuroxime OR Amoxicillin-Clavulanic acid OR Ticarcillin-Clavulanic acid OR Cefotaxime	Cefuroxime 75-240 mg/kg (max. 6 g) IV/ IM 8 hourly. Ticarcillin-Clavulanic acid 200-300 mg/kg (max. 16 g) IV 6-8 hourly.	7-10 days
Orbital cellulitis	Cefotaxime + Clindamycin OR Piperacillin-tazobactum	Piperacillin-Tazobactum 200-400 mg/kg (max. 12 g) IV 6-8 hourly. Dose as above for other drugs	2-3 weeks
Neonatal scalp/ breast abscess	Cloxacillin/ cefazolin/ clindamycin + Gentamicin/ Cefotaxime/ Ceftazidime	Dose as above. Ceftazidime 75-150 mg/kg (max. 6 g) IV/ IM 6 hourly.	7-14 days
Neonatal omphalitis	Cloxacillin + Gentamicin ± Metronidazole OR Piperacillin-Tazobactum	Dose as above for other drugs Metronidazole 20 mg /kg / day IV / oral 6-8 hourly	10-14 days
Bite wound	Ampicilln-Sulbactum OR Ticarcillin-Clavulanic acid OR Piperacillin-Tazobactum OR Ceftriaxone/ cefotaxime + Gentamicin	Dose as above for other drugs Ceftriaxone 50-100 mg/kg (max. 4 g) IV/ IM 12-24 hourly.	7-10 days
Necrotizing fascitis	Benzylpenicillin + clindamycin OR Ceftazidime + Clindamycin OR monotherapy with piperacillin/ tazobactum aminoglycoside/ metronidazole may be added.	Dose as above.	2-6 weeks
Pyomyositis	Cloxacillin/ cefazolin + clindamycin OR Vancomycin + metronidazole	Dose as above for other drugs Vancomycin 40-60 mg/kg (max. 2 g) IV 6 hourly.	2-6 weeks
Post-surgical wound infection	Piperacillin/ Tazobactum OR 3rd gen. cephalosporins + clindamycin/ metronidazole	Dose as above.	10-14 days
SSSS	Cloxacillin + gentamicin OR Clindamycin + Cefotaxime	Dose as above for other drugs Gentamicin 7.5 mg/kg (max. 300 mg) IV 8 hourly. Cefotaxime 75-225 mg/kg (max. 12 g) IV/ IM 6-8 hourly.	7-10 days
TSS	Vancomycin + low-dose Clindamycin ± gentamicin/ rifampicin	Dose as above.	7-10 days

Dosages of antibiotics mentioned are for pediatric use, with a range from minimum to maximum

with this organism.[42] Though routine screening and treatment of carriage sites are not recommended, in children with recurrent CA-MRSA infection, culture for nasal carriage should be considered.[14] In an

Indian study, *S. aureus* colonization of the anterior nares was observed in 54.4% of cases, 11.8% of which were MRSA.[8] Antibiograms of clinical isolates of *S. aureus* matched with nasal isolates in 49% of cases in the above quoted study.[8] However, in a recent study, significant discordance was found between the strains of *S. aureus* isolated from the sites of SSTIs and nasal colonization; and in the authors' opinion, recurrences of SSTIs were common but unrelated to the patients' baseline status of nasal colonization with MRSA.[43]

Treatment of only nasal carriage has little effect, and all carriage sites should be treated together.

Oral
Low-dose oral clindamycin has been used for 3 months to prevent colonization and recurrent bacterial infections in non-hospitalized patients with documented recurrent infections with MSSA.[44] However, compliance with such regimen may be poor, and drug resistance may develop easily. In India, prolonged use of clindamycin may turn out to be costly.

Topical
Application of topical mupirocin in nasal vestibule (up to tip) twice daily for 5 days/ month for consecutive 3 months has been used successfully.[45] Some authors have found a 6 week course of topical mupirocin to the nares to be effective in eliminating MRSA carriage;[12] one Indian study has used this regimen in children with success.[16]

The mupirocin formulation for nasal application is its calcium salt in white soft paraffin/ Softisan 649 base, which makes it less irritant on mucosa.[36,39] Presently it is not available in the Indian market. Intranasal application of topical fusidic acid is also effective in treating nasal carriage of *S. aureus,* and 80% eradication at 1 year has been demonstrated in one study.[46] Silver sulphadiazine is a promising agent in treating nasal colonization.[26] Gentian violet 1% has been used to treat colonization, but longer treatment duration is required to serve this purpose.[47]

Treatment of colonization with MRSA
Nasal carriage with CA-MRSA can be effectively treated with topical mupirocin, and it reduces the chances of hand-carriage of the organism as well.[14] Most systemic antibiotics used to treat widespread infections caused by MRSA attain poor concentration at sites of colonization.[14] Systemic clindamycin achieves good concentration in nasal vestibule but increasing resistance remains a concern.

Topical agents to be used to reduce surface colonization of MRSA include the following[26]:
- Hand wash with 70% alcohol
- Chlorhexidine gluconate, 4% (more active against MRSA than MSSA)
- Triclosan (soap)
- Povidone iodine (equally active against MRSA and MSSA)

Treatment failure for colonization is indicative of re-colonization rather than true treatment failure.[14]

TOXIN-MEDIATED BACTERIAL INFECTIONS OF SKIN

Staphylococcal scalded skin syndrome[1,3]
Staphylococcal scalded skin syndrome (SSSS) is caused by staphylococcal exfoliative toxin (ET) serotypes ETA, ETB and ETD, resulting in disruption of the intercellular cytoskeleton structure of epidermis, desmoglein. The same mechanism is operative in the milder form of the disease 'bullous impetigo.' and usually widespread exfoliation is prevented by the development of 'antitoxin antibodies' in sera. Lack of protective antitoxin antibodies facilitates occurrence of widespread exfoliation.

It is well documented that early administration of antibiotics halts the progression to exfoliative phase.[48] In presence of extensive exfoliation in neonates and small children, there is a risk of fatal secondary Gram-negative skin infections (particularly *P. aeruginosa*) and septicemia.[3] The affected neonates and children should be treated in isolation as burn patients. Antibacterial coverage includes antibiotics against *S. aureus* and Gram-negative organisms if secondary infection is suspected. Exfoliation usually continues till 24 to 48 hours after starting antibiotics.

Toxic shock syndrome (TSS)[3]
Staphylococcal (TSS toxin-1 and enterotoxins) and streptococcal toxins (pyrogenic toxins and mitogenic toxins), which act as superantigens, are the causative factors for TSS. Bacterial superantigen-mediated direct release of several cytokines from T-cells is responsible for myriad of symptoms like fever, scarlatiniform skin rash, hypotension, disseminated intravascular coagulation and multi-organ failure.

Supportive management with intravenous fluid and maintenance of cardiopulmonary function are the crux of therapy in TSS. Choice of intravenous antibacterial agents should aim at both *S. aureus* and *S. pyogenes.* Clindamycin should be added to other antibiotics at a lower dosage, as it has been shown to inhibit staphylococcal toxin (superantigen) production at this concentration.[49] Intravenous immunoglobulin (IVIg) has neutralizing action on the bacterial superantigens; hence treatment with IVIg is recommended to reduce the mortality associated with TSS.[50]

SSTIs are the commonest infections in Indian pediatric population and in other developing countries. These contribute to significant morbidity and increased mortality due to related complications for the future generations of India. Because of the ubiquitous occurrence and trivial nature of the lesions, parents often neglect to seek health-care facilities for superficial pyodermas. However, an episode of uncared childhood pyoderma may precipitate crippling complications like chronic glomerulonephritis or rheumatic heart disease in adult life. Hence awareness regarding the importance of medical care for common skin infections should be created among general population, like groups of women, school teachers and primary health-care workers.

Though the problem of drug resistance exists, while treating SSTIs in India, the clinicians in primary health-care setup do not have many options except empirical antibiotic treatment with available, cheaper drugs like penicillins, co-trimoxazole, erythromycin, topical gentian violet, etc. However, whenever, nonresponse to therapy is suspected, the option of referral to higher centers should be kept open. In secondary and tertiary health-care centers, there must be an attempt to identify prevalent organisms causing SSTIs in the locality and the emerging antibiotic-resistance pattern. In this regard, periodic collaborative works among all clinical departments, along with collaboration with microbiologists, are helpful. This will help to chalk out effective management protocol, keeping in mind the limited resources, for childhood SSTIs in developing countries.

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