Sulfadiazine in children
Sulfadiazine - tablet 500 mg and injection 250mg/4ml - is listed in the WHO Model List of Essential Medicines for Children in the complementary list as ‘other antibacterials’. This review is on uses, safety, efficacy and dosage of sulfadiazine in children.

Summary
Sulfadiazine is recommended as the preferred drug for the treatment of different forms of toxoplasmosis, a protozoal infection. Under ‘6.5.4 anti pneumocystis and anti toxoplasmosis medicines’ of EML only sulfamethoxazole-trimethoprim is listed. Sulfadiazine is one of the options for treating nocardiosis, an infrequent bacterial infection in children. Cotrimoxazole is preferred by some. Although sulfadiazine was used for many indications including UTI, meningococcal meningitis and prevention of rheumatic fever, it is currently not recommended for these conditions.

This drug is poorly soluble in urine and causes crystalluria more often than other sulfonamides. Recommended route of administration is oral. It is costlier compared to cotrimoxazole. Injectable formulations may not be available internationally. BNF C (2006) recommends sulfadiazine, orally, only for toxoplasmosis.

Recommendations
Shift to section 6.5.4 of EML C
Delete injection

Review
Sulfonamides are the earliest group of antibacterial medicines to be used widely for treatment. However, indications for their use decreased considerably because of increasing bacterial resistance to sulfonamides and because newer more effective drugs became available.
Pharmacokinetics [1, 2]
Approximately 70% to 100% of an oral dose is absorbed rapidly from the GI tract. Peak plasma levels are achieved in 3 to 6 hours. Following a single dose of 3 g, peak concentration is approximately 50 µg/ml. Wide variations in blood levels may occur with identical doses. In a group of infants receiving 50-100mg/day of sulfadiazine for congenital toxoplasmosis, plasma concentrations varied from 60-86 µg/ml [3]. Concentrations of 50-150 µg/ml are considered therapeutic for most infections and 120-150 µg/ml optimal for serious infections. Blood concentrations should generally not exceed 200µg/ml. About 50% of the drug is bound to plasma protein. Sulfadiazine is excreted primarily in urine, partly unchanged. Administration of alkali accelerates renal clearance. The elimination half-life is roughly 17 hours and is significantly longer in those with renal damage. Itdiffuses well into tissues and body fluids including CSF, pleural, peritoneal, synovial and ocular fluids and may reach 50% to 80% of blood levels.

Spectrum of activity
Sulfadiazine exhibits *in vitro* inhibitory activity against several aerobic gram-positive and gram-negative bacteria, *Nocardia* sp., *Actinomyces* sp., *Chlamydia trachomatis* and protozoa *Plasmodium falciparum*, and *Toxoplasma gondii*. Sulfadiazine also is active against, *Paracoccidioides brasiliensis*. However resistance to sulfonamides is widespread and increasing among bacteria like streptococci, staphylococci, Enterobacteriaceae, and *Neisseria* sp.
The cost of one 500mg tablet varies from US $ 0.0135 to 1.45 (International Drug Price Indicator Guide). Injection is not listed. Cost of cotrimoxazole tablet (200+40 mg) is US$ 0.0074

Uses
Sulfadiazine is administered orally. Adequate fluid intake to avoid crystallopathy has to be ensured. Dose needs to be adjusted in those with renal impairment.

Toxoplasmosis
Toxoplasmosis, a protozoal infection may be congenital or acquired later in life. Congenital toxoplasmosis may be asymptomatic, mild or have neurological and ocular manifestations. Acquired toxoplasmosis in the immunocompetent host, is most often
(70-90%) asymptomatic. In the immunocompromised, encephalitis (TE) is the most common manifestation [4].

There is paucity of data on the prevalence of clinical toxoplasmosis in communities. It is an important cause of posterior uveitis in immunocompetent patients [4]. In Brazil, toxoplasma retinochoroiditis was seen in 20% of children with visual impairment [5]. In a survey done in Trinidad, 0.4% of 504 cord blood samples had IgM toxoplasma antibodies, suggesting presence of disease [6].

In the pre antiretroviral therapy era, the 12-month incidence of TE was approximately 33% in patients with advanced immunosuppression, seropositive for *T. gondii* (approx 15% in the US, 50%--75% in certain European countries) and not receiving prophylaxis. The incidence has decreased substantially since then [7]

**Toxoplasma Encephalitis:** A Cochrane review (2006) on therapy for TE in adult patients with AIDS identified three studies – two comparing sulfadiazine + pyrimethamine with clindamycin + pyrimethamine and the third comparing sulfadiazine + pyrimethamine with cotrimoxazole. There were no significant differences between regimes in clinical cure rates [8]. Compared to clindamycin, sulfadiazine had better results although not significant. Another trial (2007) on 43 patients also showed sulfadiazine containing regime and co trimoxazole to be comparable[9]. However, a more recent clinical trial (2008) has concluded that sulfadiazine along with pyrimathamine and folinic acid is the best option although there was no difference in failure rates between this regime and cotrimoxazole, both given for 6 wks [10]. Pyrimethamine, sulfadiazine and leucovorin is recommended in guidelines as the preferred therapy for TE [11, 12]. The recommended dose in children and infants > 2 months is 120—200 mg/kg/day (max 6gms) orally in four divided doses for 6wks. Loading of 75mg/kg is recommended by some[4, 12, 13]

**Congenital toxoplasmosis:** Pyrimethamine, sulfadiazine and folic acid is the recommended treatment for neonates also [4, 12]. One hundred and thirty two children with congenital toxoplasmosis, treated during the first of year of life with sulfadiazine, pyrimethamine and leucovorin had lesser chance of developing new chorio retinal lesions on long term follow up [14]. Another long term follow up study (Mean age 10.5 yrs) also showed that treatment of babies with congenital toxoplasmosis with sulfadiazine and pyrimethamine for the first year of life can
considerably reduce unfavourable outcomes [15]. Other studies also support this finding [16]. Recommendation is 100 mg/kg/day orally in 2 or 4 divided doses for 12 months [4, 12].

*Active ocular toxoplasmosis:* Both sulfadiazine containing regime and cotrimoxazole preformed equally well in one RCT where all 59 patients improved equally well [17].

Sulfadiazine is therefore recommended for all forms of toxoplasmosis, in combination with pyrimethamine and folinic acid. There is some indication that in vitro resistance may be developing to this drug [18].

For secondary prophylaxis after treatment of acute TE in HIV-infected children and infants, CDC recommends 85-120 mg/kg/day orally in 2 - 4 divided doses along with pyrimethamine and leucovorin [19]. Australian Medicines Handbook also recommends for this indication.

**Nocardiosis**

Nocardia spps are susceptible to sulfonamides in vitro and are recommended as first line drugs [20]. In the US 500 to 1000 new cases occur per year and about 15% have HIV infection also [21]. Nocardiosis occurs as opportunistic infection in other conditions with immunosuppression also [22]. About 80% of those infected present as invasive pulmonary disease while 20% present as cellulites [21]. Keratitis and mycetoma are also manifestations of nocardiosis. Data on the magnitude of this infection in children is scanty. Case reports of different manifestations in children exist. In a case series, 13/15 mycetomas in children were due to nocardia spp [23]

There is no clinical data to support choice of therapy. Sulfadiazine or cotromoxazole is recommended [1, 20]. Cotrimoxazole is considered better by some authorities and judging from case reports, it is most often used for nocardiosis. It is reported as useful in a case series [24]. All isolates were susceptible in another study [25].

Treatment for cellulites is for 3-12 months[26] and that for pulmonary infection 6-12 months [20]. Sulfadiazine dosage recommended for adults is 6 to 8 g daily. A second antibiotic in addition to sulfonamide is recommended. Australian Medicines Handbook recommends sulfadiazine for this indication as well, but has only adult dosage.
Other infections
Sulfadiazine is rarely used to treat other infections like UTI due to susceptible organisms. They are no longer recommended for empirical therapy of UTI, meningococcal meningitis or shigellosis because of resistance [1]. They are no longer used for rheumatic fever prophylaxis.

It may be used for the treatment of paracoccidioidomycosis

Adverse events [1, 2]
Numerous adverse reactions to sulfadiazine have been reported and about 5% of individuals develop adverse reactions[1]. Six out of 48 infants developed neutropenia and one had elevated bilirubin in a case series. No other adverse events were noted [3]

Crystalluria - Compared with many newer sulfonamides, sulfadiazine is less soluble and more likely to crystallize in concentrated acidic urine, especially in dehydrated patients and in those with impaired renal function. Crystallopathy and acute renal failure can develop [27]. Adequate fluid intake can help to minimize crystalluria and the subsequent development of renal failure.

Blood dyscrasias - Agranulocytosis can occur in 0.01% patients on sulfadiazine. Aplastic anemia is rare, but more frequent in patients with AIDS. Acute hemolytic anemia is more likely to occur in individuals with glucose-6-phosphate dehydrogenase deficiency, but is less frequent with sulfadiazine (0.05%). Thrombocytopenia and leukopenia can also occur. Complete blood counts should be monitored and the drug discontinued if abnormalities occur.

A serious, but infrequent adverse effect of sulfadiazine is methemoglobinemia.

Hypersensitivity - A variety of skin manifestations like rash, erythema multiforme, toxic epidermal necrolysis, Steven Johnson syndrome etc can occur. Hepatitis, and anaphylactoid reactions are reported. The overall incidence of allergic reactions to sulfadiazine may be higher in HIV-infected patients than in non-HIV-infected individuals

Gastrointestinal adverse effects reported with sulfadiazine include abdominal pain, anorexia, diarrhea, nausea/vomiting, pancreatitis, and stomatitis.

Kernicterus - The administration of sulfonamides to newborn infants, especially if premature, can lead to the displacement of bilirubin from plasma albumin causing kernicterus. Reports of this complication are extremely rare.
Drug interactions especially with anticonvulsants and anticoagulants can occur.

Drug fever has been reported with sulfadiazine

References
7. MMWR, Treating Opportunistic Infections Among HIV-Infected Adults and Adolescents Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. 2004. 53 (RR 15); 1-112.


19. MMWR, Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons


21. CDC, Nocardiosis. Disease listing.


