

DRUG RESISTANCE IN *SALMONELLA ENTERICA* SEROTYPE TYPHI AND PARATYPHI A

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Abstract: Enteric fever continues to be a major health problem due to poor hygiene and sanitary conditions prevalent in developing countries like India. Transmission occurs when susceptible individuals ingest contaminated food or water. The prognosis for a patient depends on the rapidity of diagnosis and appropriate and timely treatment. But the fact that this bacterium is rapidly becoming resistant to commonly used antibiotics is of great concern. Plasmid-mediated antibiotic resistance against 1st line anti-typhoid drugs like ampicillin, chloramphenicol, and co-trimoxazole and chromosomal resistance to the fluoroquinolones have reduced therapeutic options in this completely treatable disease. Irrational usage of antimicrobials in humans as well as in live stock could be attributable to the development of resistance.

INTRODUCTION

Enteric fever continues to be a major public health problem especially in developing countries despite the availability of effective antimicrobials for treatment. It is an acute systemic illness caused by infection with various serovars of *Salmonella enterica* serotype Typhi (*S. typhi*) and *Salmonella enterica* serotype Paratyphi A (*S. paratyphi* A). Timely treatment with appropriate antimicrobial agents is important in reducing the mortality due to *Salmonella typhi* and *Salmonella Paratyphi A* from 30% to as low as 0.5%¹.

Transmission most commonly occurs when susceptible individuals ingest contaminated food or water. The food handlers prominently play a role in disseminating typhoid bacilli through different food products and water. In endemic areas identified risk factors for disease include eating food prepared out side the home, such as ice cream or flavored iced drinks from street vendors².

EPIDEMIOLOGY

Enteric fever is a major public health problem in the developing countries. It affects 16 million people worldwide with more than 600,000 deaths a year. Almost 80% of the cases and deaths are in Asia and the rest occur mostly in Africa and Latin America³. In developed countries, this disease has been virtually eliminated. This progress is achieved through improved food handling practices and water treatment. The peak incidence is reported in children between 5 and 19 years of age in developing countries and the majority of the cases are occurring in travelers returning from endemic areas. But some studies in South Asia report highest rates of enteric fever under 5 years of age^{4,5}.

PATHOGENESIS

The infectious dose of *S. typhi* varies between 1000 and 1 million organisms. The incubation period is usually 7 to 14 days. On ingestion, after bypassing the gastric acidity, the organisms invade the intestinal epithelium through the Peyer's patches. After penetration, they translocate to the intestinal lymphoid follicles and mesenteric lymph nodes and even to the reticuloendothelial cells of the liver and spleen where they multiply and reach the blood stream referred to as "primary blood stream invasion". The bacteria get seeded in several reticuloendothelial sites and spill over from these sites into the bloodstream causing secondary bacteremia and the patient now begins to present with symptoms⁶. The organisms are then widely disseminated into liver, spleen, bone marrow, gall bladder and Payer's patches of terminal ileum.

CLINICAL FEATURES

Most patients who present to hospitals with typhoid fever are children or young adults. But many patients especially children under five years of age may present with nonspecific symptoms. Patients usually presents with fever with chills, headache, malaise, anorexia, nausea, abdominal discomfort, dry cough and myalgia. Abdominal symptoms may vary, young children usually present with diarrhoea but adults often present with constipation.⁷ On examination, a coated tongue, tender abdomen and hepatosplenomegaly are the common findings.⁷ A relative bradycardia may also be common. Convulsions may occur in children under five years of age. Complications occur in 10-15% of patients, the most important of which are gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy⁸. Relapse occurs in 5-10% of patients, usually two to three weeks after the resolution of fever and may be distinguished from re-infection by molecular typing. Long term carrier rate is 1 to 4 percentage. The average case fatality rate is less than one percent. The case fatality rates are highest among children under one year of age and among the elderly⁹. The most important contributor to a poor outcome is probably a delay in instituting effective antibiotic treatment⁸.

LABORATORY DIAGNOSIS

Haematological investigations are usually nonspecific. The hemoglobin level, white cell count, and platelet count are usually normal or reduced. The liver enzymes are usually raised. The definitive diagnosis of enteric fever requires the isolation of *S. typhi* or *S. paratyphi* from blood, bone marrow, urine, bile, gastric or intestinal secretions. Blood cultures have a sensitivity of 40-60%, usually early in the course of the disease¹⁰. Stool & urine cultures become positive after the first week of infection, but their sensitivity is much lower. Although bone marrow cultures have a greater sensitivity of 80% to 95%, they are difficult to obtain and are relatively invasive⁸. The classic widal test, although simple to perform, lacks sensitivity and specificity. Newer diagnostic tests such as Typhidot or Tubex which directly detects IgM antibodies against a host of *S. typhi* antigens also lacks sensitivity (84-93%) and specificity (77-89%). A nested polymerase chain reaction using H1-d primers has been used to amplify specific genes of *S. typhi* in the blood of patients and is promising means of making a rapid diagnosis¹¹.

TREATMENT

Early diagnosis and prompt antimicrobial therapy are essential for

optimal management of enteric fever, especially in children. Although most cases can be managed at home with oral antibiotics and regular follow-up for development of complications and failure of therapy, patients with severe illness, persistent vomiting, severe diarrhea and abdominal distension require hospitalization and parenteral antibiotic treatment. In addition to antibiotics, supportive therapy and maintenance of fluid, electrolyte and nutrition are essential. Recommended antibiotic treatment for typhoid fever is given in Table 1 & 2^{10,11}.

Table 1: Recommended antibiotic treatment for uncomplicated enteric fever (adapted from WHO and Bhutta)^{32,33}

Susceptibility	Optimal treatment			Alternative treatment		
	Drug	Daily dose(mg/kg)	Days	Drug	Daily dose(mg/kg)	Days
Fully sensitive	Fluoroquinolone (such as ofloxacin or ciprofloxacin)	15	5-7	Chloramphenicol	50-75	14-21
				Amoxicillin	75-100	14
				Co-trimoxazole	8-40	14
Multidrug resistance	Fluoroquinolone or	15	5-7	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistance	Azithromycin or	8-10	7	Cefixime	20	7-14
	Ceftriaxone	75	10-14			

Table 2: Recommended antibiotic treatment for severe enteric fever (adapted from WHO and Bhutta)^{32,33}

Susceptibility	Optimal treatment			Alternative treatment		
	Drug	Daily dose(mg/kg)	Susceptibility	Drug	Daily dose(mg/kg)	Days
Fully sensitive	Fluoroquinolone	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	14
				Co-trimoxazole	8-40	14
Multidrug resistance	Fluoroquinolone	15	10-14	Ceftriaxone or	60	10-14
				Cefotaxime	80	10-14
Quinolone resistance	Ceftriaxone or	60	10-14 days	Fluoroquinolone	20	14
	Cefotaxime	80	10-14 days			

ANTIMICROBIAL RESISTANCE

Chloramphenicol was introduced in 1948 as the first effective antibiotic in the treatment of typhoid fever¹². Even though resistance started to develop within two years of its introduction, it did not emerge as a major problem until 1972¹³. Chloramphenicol resistance was associated with high molecular weight, self-transferable, *Inc HI* plasmids. Amoxicillin and co-trimoxazole were effective alternatives till the development of multidrug resistant (MDR) strains (resistant to ampicillin, chloramphenicol and co-trimoxazole-ACCo) towards the end of 1980s and 1990s¹³. Although initially, individual plasmids were known to code for resistance to each of these antibiotics, since 1988 a single plasmid was known to code for multidrug resistance. This 100,000 to 120,000 kD plasmid belongs to the incompatibility group H1 and is highly transmissible. The multidrug resistant plasmids were transferred by 66.6% strains during a conjugative recombination study¹⁴. Resistance rarely emerges during the course of treatment. In the Indian subcontinent and China, the frequency of these MDR strains ranged from 50% to 80%.⁷ MDR *Salmonella typhi* are still common in many areas, although in some regions fully sensitive strains have re-emerged^{15,16,17,18}. Chande et al reported the decline of MDR *S. typhi* from 92% to 22% in the same region¹⁹. Last 10 years data of *S. typhi* isolates from our hospital out-patient section also

share the same observation of reduction in ACCo resistance from 36% in 1999 to 8% in 2008. (Table 3)

Table 3: Percentage Resistance of *S. typhi* – Blood isolates-OPD at SGRH

Antimicrobial agent	% Resistance in each year									
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Ampicillin	36	35	35	24	26	24	18	19	17	8
Chloramphenicol	36	33	35	28	26	24	19	14	12	10
Co-trimoxazole	36	36	26	32	23	24	28	23	27	24
Nalidixic acid	-	-	-	-	51	65	91	86	91	93
Ciprofloxacin	0	0	0	0	0	0	1.08	6	7	23
Ceftriaxone	0	0	0	0	0	0	0	0	0	0
Cefixime	-	-	-	-	-	-	-	0	0	0

The fluoroquinolones (ciprofloxacin and ofloxacin), third generation cephalosporins (ceftriaxone & cefixime) and azithromycin came up as the 2nd line of treatment for MDR strains.

Fluoroquinolones have good in vitro activity against salmonellae and became the treatment of choice in cases of MDR salmonellosis²⁰. The fluoroquinolones effectively penetrate macrophages and achieve high concentrations in bile. Some randomized controlled trials have shown that fluoroquinolones, when compared with ceftriaxone, cefixime and first-line antimicrobials have lower clinical failure rates and lower fever clearance times in the treatment of enteric fever. They also have the advantage of lower rates of stool carriage than the first line drugs⁸.

Rampant use of ciprofloxacin not only for typhoid but also for other infections and also their subsequent licencing for usage in animals gradually led to increase in minimal inhibitory concentration (MIC) of this drug. Since the early 1990s, reports have been coming up of nalidixic acid resistant *S. typhi* infections that did not respond to ciprofloxacin therapy, despite the organisms having MIC values within the susceptible range. Those strains were demonstrated to have MIC values for ciprofloxacin higher (0.125 to 1 µg/ml) compared with the usual values of fully susceptible strains (<0.125 µg/ml)^{21,22,23,24}. In 1997, these observations made in case reports were extended by a typhoid fever treatment trial of ofloxacin. The study of short course (2-3 days) ofloxacin therapy conducted in Vietnam for uncomplicated typhoid fever included 117 patients infected with MDR *S. typhi*. All *S. typhi* isolated had MICs of ofloxacin $\leq 1\mu\text{g/ml}$. The median time to fever clearance was 156 h for patients infected with nalidixic-acid resistant *S. typhi* and 84 h for those infected with nalidixic-acid susceptible *S. typhi*. Furthermore, 33% of nalidixic-acid resistant *S. typhi* infections required re-treatment, whereas 0.8% of infections caused by susceptible strains required re-treatment. The authors of this report recommended that short courses of fluoroquinolone therapy should not be used for patients with nalidixic-acid resistant *S. typhi*. Further nalidixic-acid resistant *S. typhi* infections had unsatisfactory responses to treatment even with a full 7-10 day course of ofloxacin.²⁵ Thus nalidixic acid resistance among *S. typhi* and *S. paratyphi A* can be used to identify strains with reduced susceptibility to fluoroquinolones. In our hospital, since April 2003, after noticing inadequate response to treatment with quinolones, nalidixic acid susceptibility testing was started routinely for all *Salmonella* isolates. Nalidixic acid resistant *Salmonella* isolates were found to have almost tenfold higher MIC to ciprofloxacin.²⁴ The first high-level ciprofloxacin resistant (defined as MIC $\geq 4\mu\text{g/ml}$) strain was isolated in our hospital in July 2005 with an MIC of $>32\mu\text{g/ml}$.¹⁷ Subsequently the number of ciprofloxacin resistant isolates were showing a gradual rise in the subsequent years (Table 3&4).

Table 4: Percentage Resistance of *S. paratyphi A* – Blood isolates-OPD at SGRH

Antimicrobial agent	% Resistance in each year									
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Ampicillin	0	4	0	0	0	0	0	0	0	4
Chloramphenicol	0	0	0	0	0	0	0	0	0	0
Co-trimoxazole	0	0	0	0	0	0	0	0	0	2
Nalidixic acid	-	-	-	-	79	85	98	98	98	100
Ciprofloxacin	0	0	0	0	0	0	0	2	2	0
Ceftriaxone	0	0	0	0	0	0	0	0	0	0
Cefixime	-	-	-	-	-	-	-	0	0	0

Quinolone resistance is mediated by nontransmissible, spontaneously occurring point mutations in chromosomal genes (*gyrA*, *gyrB*, *parC* and *parE*). These point mutations alter the enzymes, DNA gyrase and topoisomerase IV that are targets for quinolone drugs. The most frequent mutation is a single-point mutations in the *gyrA* gene, characteristically occurring at position 83 of the DNA gyrase enzyme (changing serine to phenylalanine) and position 87 (changing aspartate to tyrosine or glycine)²⁶. Although altered permeability of bacterial cell membranes and efflux pumps are not well understood, these mechanisms also play a role in quinolone resistance for some isolates and are not known to be transmissible. Until recently, quinolone resistance was believed to arise solely from chromosomal mutations in genes encoding target enzymes or due to decreased accumulation of the drug inside the bacteria. In 1998, mobile elements with the potential for horizontal transfer of quinolone resistance genes were described²⁷. The locus responsible for this plasmid mediated quinolone resistance, designated *qnr A*, *qnr B* and *qnr S*, has been identified in Enterobacteriaceae species. The *qnr A* gene confers nalidixic acid and low level fluoroquinolone resistance and its presence has been shown to facilitate selection of chromosomal mutations that confer higher levels of resistance. This plasmid mediated quinolone resistance was unknown in *Salmonella enterica* until recently. There is a report of plasmid-mediated quinolone resistance in non-Typhi serotypes of *Salmonella enterica* carrying either *qnr B* or *qnr S* from United States.²⁸ Plasmid mediated quinolone resistance in *Salmonella* is of great concern, since horizontal transfer of quinolone resistance would facilitate rapid dissemination of the quinolone resistance genes, further compromising the use of these antimicrobial agents.

In the recent past, 3rd generation cephalosporins have gained importance for the treatment of enteric fever because of their pharmacodynamic properties and the very low prevalence of resistance to these agents. Ceftriaxone administered either intravenously or intra-muscularly and cefixime which is administered orally are both effective in typhoid fever and are commonly used in the treatment. Cefotaxime and cefoperazone are other treatment options. Since 1991, non-typhoidal salmonella species resistant to extended-spectrum cephalosporins have been reported in several countries including Argentina, Turkey, Algeria, Saudi Arabia, Greece, Tunisia and France²⁹. Extended spectrum cephalosporin resistance in *Salmonella* strains is usually due to the production of plasmid-mediated extended-spectrum β -lactamases or AmpC β -lactamases, and among these β -lactamases, the CMY-2 AmpC enzyme has been reported most often³⁰. But surveillance data from many countries world wide shows that ceftriaxone resistance still remains low all

over the world. There have been sporadic reports of high-level resistance to ceftriaxone (MIC 64 $\mu\text{g/ml}$) in *S. enterica* serotype typhi and *S. enterica* serotype paratyphi A although these strains are very rare. All isolates in our hospital has been sensitive to ceftriaxone and cefixime (Table 3&4).

The azalide antimicrobial azithromycin is also an option in the treatment of MDR enteric fever. Treatment courses of 500 mg per day for 7 days and 1g per day for 5 days have proven successful for adults and children including nalidixic acid resistant infections³¹. In vitro, azithromycin has an MIC range of 4 to 16 $\mu\text{g/ml}$ against *S. typhi*, suggesting that the drug has limited utility for the treatment of typhoid fever. However, azithromycin is highly effective in clearing the infection probably because of the remarkable property of intracellular concentration (50 to 100 times that in serum) of this antibiotic. A combination of fluoroquinolone with azithromycin may improve the efficacy compared with the fluoroquinolone alone and potentially reduce the chance of fluoroquinolone resistant mutants emerging³².

Aztreonam and Imepenem are also potential third line drugs that have been used recently in serious infections⁸.

PREVENTION OF EMERGING DRUG RESISTANCE

Epidemiologic investigations have demonstrated that the use of antimicrobial agents in livestock is the principal cause of emergence and dissemination of resistance to antimicrobial agents in strains of nontyphoidal salmonella³³. The implementation of appropriate safeguards including restricting the use of certain antimicrobial agents in livestock, may slow the evolution of antimicrobial resistance in salmonella and prevent the transmission of resistant strains of salmonella from livestock to humans.

CONCLUSION

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and appropriate antibiotic treatment. But the fact that both *S. typhi* and *S. paratyphi* are rapidly becoming resistant to commonly used antibiotics is of great concern. Considering the paucity of effective antimicrobial in pipeline, the focus has to be on safe water and sanitation services, community education, control on over use and misuse of antimicrobial agents and large scale vaccination strategies.

REFERENCES

1. **Edelman R, Levine MM.** Summary of an international workshop on typhoid fever. *Rev Infect Dis* 1986; 8:329-49.
2. **Black RE, Cisneros L, Levine MM, Banfi A, Lobos H, Rodriguez H.** Case-control study to identify risk factors for paediatric endemic typhoid fever in Santiago, Chile. *Bull World Health Organ* 1985;63:899-904.
3. **The World Health Report, Report of the Director General WHO.** World Health Organization: Geneva; 1996.
4. **Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B et al.** Typhoid fever in children aged less than 5 years. *Lancet* 1999;354:734-7
5. **Saha SK, Baqui AH, Hanif M, Darmstadt GL, Ruhulamin M, Nagatake T et al.** Typhoid fever in Bangladesh: implications for vaccination policy. *Pediatric Infectious Diseases Journal* 2001;20(5):521-4
6. **House D, Bishop A, Parry CM, Dougan G, Wain J.** Typhoid fever: pathogenesis and disease. *Curr Opin Infect Dis* 2001;14:573-8
7. **Lee TP, Hoffman SL.** Typhoid fever. In: Strickland GT editor (s). *Hunter's Tropical Medicine and emerging infectious diseases.* 8th Edition. Philadelphia, London: Saunders, 2000:471-83.
8. **Parry CM, Hien TT, Dougan G, Whittle NJ, Farrar JJ.** Typhoid fever. *New England Journal of Medicine* 2002;347(22):1770-82.

9. **Butler T, Islam A, Kabir I, Jones PK.** Patterns of morbidity and mortality in typhoid fever dependent on age and gender: a review of 552 hospitalized patients with diarrhoea. *Rev Infect Dis* 1991;13:85-90.
10. **World Health Organization.** Department of Vaccines and Biologicals. Background document: the diagnosis, prevention and treatment of typhoid fever. Geneva: WHO. 2003:19-23
11. **Bhutta ZA.** Current concepts in the diagnosis and treatment of typhoid fever. *British Medical Journal.* 2006;333:78-82.
12. **Woodward TE, Smadel JE, Ley HL Jr, Green , Mankikar DS.** Preliminary report on the beneficial effect of chloramphenicol in the treatment of typhoid fever. *Ann Intern Med* 1948; 29:131-4.
13. **Mizra SH, Beeching NJ, Hart CA.** Multi-drug resistant typhoid: a global problem. *J Med Microbiol* 1996; 44:317-9.
14. **Setnthilkumar B and Praphakaran G.** Multidrug resistant *Salmonella typhi* in asymptomatic typhoid carriers among food handlers in Namakkal district, Tamil Nadu. *Indian Journal of Medical Microbiology.*2005;23(2):92-94.
15. **Sood S, Kapil A, Das B, Jain Y, Kabra SK.** Re-emergence of chloramphenicol-sensitive *Salmonella typhi*. *Lancet* 1999;353:1241-2
16. **Wasfy MO, Frenck R, Ismail TF, Masour H, Malone JL, Mahoney FJ.** Trends of multiple-drug resistance among *Salmonella* serotype Typhi isolates during a 14-year period in Egypt. *Clinical Infectious Diseases* 2002;35(10):1265-8.
17. **Raveendran R, Watal C, Sharma A, Oberoi JK, Prasad KJ & Datta S.** High level Ciprofloxacin resistance in *Salmonella enterica* isolated from blood. *Indian Journal of Medical Microbiology* 2008;26(1):50-3.
18. **Krishnan P, Stalin M, Balasubramanian S.** Changing trends in antimicrobial resistance of *Salmonella enteric* serovar typhi and *Salmonella enteric* serovar paratyphi A in Chennai. *Indian Journal of Pathology and Microbiology* 2009;52(4):505-8
19. **Chande C, Shrikhande S, Kapale S, Agarwal S, Fule RP.** Change in antimicrobial resistance pattern of *Salmonella typhi* in central India. *Indian J Med Res* 2002;115:46-8.
20. **Pegues DA, Ohl ME, Miller mSI.** *Salmonella* species, including *Salmonella Typhi*. In: *Principles and practice of infectious diseases.* 6th ed. Mandell GL, Bennet5t JE, Dolin R, editors. Churchill Livingstone: New York; 2005.p.2636-54.
21. **Mehta G, Randhawa VS, Mohapatra NP.** Intermediate susceptibility to ciprofloxacin in *Salmonella typhi* strains in India. *Eur J Clin Microbiol Infect Dis* 2001;20:760-1
22. **Dutta P, Mitra U, Datta S et al.** Ciprofloxacin susceptible *Salmonella typhi* with treatment failure. *J Trop Pediatr* 2001; 47:252-3
23. **Kapil A, Renuka, Das B.** Nalidixic acid susceptibility test to screen ciprofloxacin resistant in *Salmonella typhi*. *Indian J Med Res* 2002;115:49-54.
24. **Joshi S, Watal C, Sharma A, Oberoi JK, Prasad KJ.** Quinolones-drug of choice for enteric fever? *Indian J Med Microbiol* 2004;22:271-2.
25. **Wain J, Hoa NTT, Chinh NT et al.** Quinolone-resistant *Salmonella typhi* in Viet Nam: molecular basis of resistance and clinical response to treatment. *Clin Infect Dis* 1997;25:1404-10.
26. **Brown JC, Shanahan PM, Jesudason MV, Thomson CJ, Amyes SG.** Mutations responsible for reduced susceptibility to 4-quinolones in clinical isolates of multi-resistant *Salmonella typhi* in India. *J Antimicrob Chemother* 1996;37:891-900
27. **Martinez- Martinez L, Pascual A, Jacoby GA.** Quinolone resistance from a transferable plasmid. *Lancet* 1998;351:797-9.
28. **Gay K, Robicsek A, Strahilevitz J, Park CH, Jacoby G, Barrett TJ et al.** Plasmid mediated quinolone resistance in non-typhi serotypes of *Salmonella enteric*. *Clin Infect Dis* 2006;43:297-304.
29. **Rossi A, Lopardo H, Woloj M et al.** Non-typhoid *Salmonella* spp. Resistant to cefotaxime. *J Antimicrob Chemother* 1995;36:697-702.
30. **Winokur PL, Brueggemann A, Desalvo DL, Hoffmann L, Apley MD, Uhlenhopp Ek et al.** Animal and human Multidrug-resistant, cephalosporin-resistant *Salmonella* isolates expressing a plasmid-mediated CMY-2 AmpC β -lactamase. *Antimicrob Agents Chemother.* 2000;44:2777-83.
31. **Girgis NI, Butler T, Frenck RW, Sultan Y, Brown FM, Tribble D and Khakhria R.** Azithromycin versus Ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrob. Agents Chemother.*1999;43:1441-1444.
32. **Parry CM, Ho VA, Phuong LT, Bay PVB, Lanh MN et al.** Randomized controlled comparison of ofloxacin, azithromycin and ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrob Agents Chemother.* 2006;51(3):819-825.
33. **van den Bogaard AE, Stobberingh EE.** Antibiotic usage in animals: impact on bacterial resistance and public health. *Drugs* 1999;58:589-607.

LITERATURE REVIEW

Initiation of dialysis at higher GFRs: Is the apparent rising tide of early dialysis harmful or helpful?

Steven Jay Rosansky et al Kidney International 2009,76,257-261.

Over the past decade a trend of increasing estimated glomerular filtration rate (eGFR) at the initiation of dialysis for treatment of end-stage renal disease (ESRD) has been noted in the United States. In 1996, only 19% of patients began dialysis therapy with an eGFR of greater than 10 ml/min/1.73m² (denoted as 'early start'), but by 2005 the fraction of early start dialysis patients had risen to 45%. This review examines US dialysis data, national guidelines, and publications relevant to the early start phenomenon. It is not known whether early start of dialysis is beneficial, harmful or neutral with respect to the outcome of dialysis treatment for ESRD. Available data indicate that mortality while on dialysis therapy may be higher in those subjects with early start. Comorbidities present at the time of dialysis initiation do not appear to be a major driving force for early start patients. As well, residual kidney function in these patients is a major contributor to total urea or creatinine clearance. This can be a positive factor for patient outcomes and might be compromised by early start. Finally, we estimate the dollar cost of early start to the US Medicare-supported ESRD program. Properly designed, prospective and randomized studies may help to clarify the benefit or harm of early start of dialysis for ESRD.

Liver Transplantation in India: The Past, Present and Future: A.S. Soin

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Liver transplantation (LT) in India, a distant dream till 1998 has now become a well established and highly successful procedure. Presently, 400 liver transplants are done annually of which 40% cases are done in Sir Ganga Ram Hospital, Delhi. Initially, the cadaveric LT was done but this did not pick up due to social and administrative problems. So, the focus shifted to living donor transplantation. Till date, we have performed nearly 463 liver transplants and doing 140 cases annually. Our current success rate is over 95%, amongst highest in the world. The marked improvement in our results has been due to team efforts of experts in transplant surgery, hepatology, anaesthesia and critical care, transfusion medicine, chest medicine, nephrology, diagnostic and therapeutic radiology, etc. Any patient with acute or chronic liver disease that leads to the inability to sustain a normal quality of life or that results in life-threatening complications should be considered a candidate for LT. The indications include fulminant hepatic failure (King's college criteria) and chronic liver disease (MELD score >15, CTP score >9, HRS, SBP, refractory ascites, recurrent HE). LT can be done in HCC with no extrahepatic spread. Currently accepted absolute contraindications to LT by most programs include HIV positivity, spontaneous bacterial peritonitis (SBP) or other active infection, severely advance cardiopulmonary disease, extrahepatic malignancy that does not meet cure criteria, active alcohol or substance abuse, and inability to comply with immunosuppression protocols because of psychosocial situations.

For LT to become more popular and accessible, we need to train more transplant experts, cut down the cost of procedure by using more indigenous medicines and equipment, involve insurance companies and also promote decreased organ donation through proposed Government of India National Organ Transplant Programme.

ERRATA

JIMSA Vol.22, Issue No. 4 Oct.-Dec. 2009 Page No. 230 Article: **Minimally Access Techniques For Menorrhagia**, the names of the authors may please be read as S.S. Trivedi, Monika Madaan (not S.S. Trivedi, Monika Nagpal).

The error is regretted.

Editor, JIMSA