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FROM THE EDITOR'S DESK

On behalf of the Editorial Board and Journal Committee of IJPP we thank all our readers for their continued support and suggestions for making this journal more popular day by day. We have introduced abstract, keywords and points to remember in all the leading articles from this issue for the purpose of indexing. We are glad to inform you that IJPP has been indexed in Excerpta Medica since January 2003. It is our prime duty now to maintain the academic standard and good scientific content in all our future issues, which will help us to get indexed in many other indexing agencies. The articles submitted for publication are being properly peer reviewed and scrutinized before being published in the journal.

This issue will focus on "Infectious Diseases in Pediatric Practice". The topics were carefully chosen with the suggestions from the journal committee by Dr.P.Ramachandran, Assistant Professor of Pediatrics, Institute of Child Health & Hospital for Children, Chennai. He has taken utmost care in selecting the topics for practitioners as well as to the academicians. We are sure our readers will definitely find these topics useful in their day-to-day practice.

The article on nosocomial infections written by Dr.Raju C Shah has clearly stressed the issues on the prevention and management of nosocomial infections in hospital practice.

Dr.Y.K.Amdekar has highlighted the treatment strategies on pneumonia in children and stressed that guidelines must be followed in general, though modified to suit special situations if necessary.

The articles on dengue illness and management of complicated malaria will bring more information to our readers during special situations. Dr. Ashok S Kapse and Dr. C.V. Vidyashankar have mentioned in their articles that awareness and familiarity with the course of the disease and its complications will certainly help in the reduction of mortality.

The article on newer cephalosporins by Dr. Niranjan Shendurnikar has focused on the properties, indications and the role of fourth generation cephalosporins as follow-up agents.

The strategies for control of infectious diseases is well discussed by Dr.S. Noel Narayanan.

We thank all the authors who have contributed articles in this issue with their rich clinical expertise and knowledge. We welcome your suggestions and feedback to improve our self to serve you better.

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Table 1. Specific infection site distribution in pediatric intensive care unit patients (NNIS* 1992- 1997)

Infection	Percentage of selected major site by age			
	Less than 2 months	More than 2 mo. and less than 5 months	More than 5 mo. and less than 12 months	More than 12 months
Blood stream infection				
- Laboratory confirmed bloodstream infection	93	92	91	93
- Clinical sepsis	7	8	9	7
Pneumonia	100			
Urinary tract infection				
- Symptomatic UTI	79	83	81	71
- Asymptomatic UTI	19	16	18	28
- Others	2	1	1	1
Surgical site infection				
- Skin	58	32	31	35
- Intra-abdominal abscess	7	23	28	23
- Soft tissue	15	17	17	20
- Mediastinitis	16	12	3	3
- Meningitis	3	12	11	10
- Others	1	4	10	9
Eye, ear, nose and throat inf.				
- Sinusitis	3	20	51	55
- Ear	8	33	11	15
- Conjunctivitis	33	16	8	6
- Other eye infections	30	4	5	2
- Upper Resp.tract infection	16	18	11	12
- Oral	16	18	11	12
Cardiovascular infections				
- Vascular	50	77	79	100
- Endocarditis	45	13	21	0

* NNIS - National Nosocomial Infection Surveillance, USA

published by some of the NICU centers do not reflect the situation of such infections in India[4,5].

Nosocomial infection rates in children: In general, overall nosocomial infection rate among pediatric patients is lower than those among the adult patients. Rate of infection is higher in children 12 months of age or younger and are particularly high among infants in neonatal ICUs (NICUs). These vulnerable patients often have

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many of the risk factors that predispose patients of all ages to nosocomial infections like severe underlying illness, loss of skin integrity or the presence of multiple devices that breach normal defensive mechanisms against potential pathogens (e.g. an endotracheal tube bypassing the mucociliary escalator). There are, however, several special aspects to the epidemiology of pediatric nosocomial infections. One is the site distribution of the infection. The blood stream is the most frequent site of infection reported in children as contrast to urinary tract in adults. (Table1). Other sites are pulmonary system, urinary tract, gastrointestinal tract, ear, eye, nose or throat, skin or soft tissue and cardiovascular system.

Pathogens involved

This is another area of difference from adult nosocomial infection. Children are at greater risk of viral infection and survey of pediatric nosocomial infection that does not include viruses will underestimate the rate. Outbreaks of nosocomial respiratory tract infection due to respiratory syncytial virus and adenovirus, of gastrointestinal tract infection due to rotavirus and hepatitis A virus and of varicella zoster in NICUs are well described in most surveys. Bacteria account for between 65 - 70%(Gram positive 50%, Gram negative 18%) of pediatric nosocomial infection, viruses for up to 25% (the majority causing gastrointestinal infection) and

Table 2. Commonly reported pathogens from patients in pediatric intensive care units by site (NNIS 1992-1997)

Pathogens	Blood Stream Infection % (n=1887)	Pneumonia % (n=1459)	Urinary Tract Infection % (n-1045)	Lower Resp. Tract Infection % (n=935)	Surgical Site Infection % (n=544)
Coagulase negative Staphylococci	37.8	0.9	4.3	1.5	14.0
Enterococcus	11.2	1.0	10.0	1.2	8.1
Staphylococcus aureus	0.3	16.9	1.5	18.8	20.2
Enterobacterial spp.	6.2	9.3	10.3	12.2	8.1
Candida albicans	5.5	1.6	14.3	3.6	5.0
Pseudomonas aeruginosa	4.9	21.8	13.1	15.1	14.5
Klebsiella pneumoniae	4.1	5.3	7.3	3.5	3.7
Other candida	3.4	0.4	6.2	1.1	2.0
Escherichia coli	2.9	3.6	19.0	3.2	5.1
Acinetobacter spp.	2.0	3.1	0.4	3.3	0.7
Serratia marcescens	2.0	3.6	1.2	3.6	2.8
Streptococcus pneumo.	–	3.4	–	2.6	0.6
Citrobacter	0.5	0.5	4.3	1.1	1.8
Candida glabrata	0.4	–	0.6	–	0.0
Other fungi	0.2	0.7	1.6	0.1	0.2
Group B streptococcus	0.1	0.2	0.1	–	0.4
Hemophilus influenzae	0.1	10.2	–	5.8	0.9
Aspergillus	0.1	0.5	–	0.1	0.7
Viruses	0.1	2.3	0.2	10.1	0.0

fungi for 5 %. The distribution of pathogens varies according to the pediatric services (Table –2), the age of the patient and the site of infection. For example, coagulase negative staphylococci (e.g. S.epidermidis) are particularly associated with implant infections (most often intravascular catheters) and infections related to intravascular catheters are responsible for 5-6 % of pediatric nosocomial infection[6].

Unique aspects of nosocomial infection in children

Host factors: Host factors that make children particularly vulnerable to infection are immaturity of immune system and congenital abnormalities. Immune deficiency are greatest in prematurely born infants, who may be hospitalised for prolonged periods of time and exposed to intensive monitoring and supportive therapies and procedures[7]. Rates of hospital acquired infection as high as 7 to 25 % are reported in neonatal intensive care units[8]. Children with congenital anomalies have a high risk of nosocomial infection because they require prolonged hospitalization, need multiple operations and have extended exposure to invasive supportive and monitoring equipments.

Sources: Important source of nosocomial infections in infants and children include the mother, invasive monitoring and supportive equipments, blood products, infant formula and expressed human milk, health care personnel and other children. Maternal infection with Neisseria gonorrhoeae, syphilis, human immunodeficiency virus, hepatitis B or herpes simplex virus poses enormous threats to the newborn. During perinatal care, procedures such as fetal monitoring with scalp electrodes, fetal transfusion and surgery, umbilical cannulation and circumcision are risk factors for infections. Infant formulas prepared in contaminated blenders or improperly stored or handled resulted in sporadic and epidemic infections in the nursery. Human milk that has been contaminated by maternal flora or by organisms transmitted through breast pumps has caused serious isolated cases of infection and epidemic disease. The risks of neonatal hepatitis and cytomegalovirus infection through human milk warrant further caution for handling.

Transmission: The transmission of microbes among children and between children and health care workers are common. Rooms crowded with children, parents and health care workers are common. Toddlers usually share rooms, waiting room, playroom, toys, books and other items and therefore have the potential of spreading pathogens directly to one another. In one study 17% of preschool children hospitalised for more than one week had a nosocomial viral respiratory tract illness. Infection of pediatric health care workers also is common. Routine care of infants and smaller children involves holding, kissing, wiping noses, feeding and changing diapers. Respiratory syncytial virus can be spread in secretions that are then inoculated into the eyes and noses of health care workers. A source of further concern involves health care workers with milder symptoms who unknowingly become intermediary hosts and who transmit infection like Bordetella pertussis to susceptible children.

It is apparent that controlling nosocomial infections is of major importance. It is also obvious that the infections among patients, hospital staff and the hospital environment that result in nosocomial infection are complex and the infection control measures must extend into many facets of the pediatric hospital or ward[9]. The aim of effective infection control are: a) to prevent patients from acquiring infection in hospital, b) to provide adequate hospital care for patients entering hospital with a community acquired infection while preventing its dissemination to others. In order to do this it is essential that each hospital should have an infection control team.

Control of infection in hospital requires an enthusiastic, able and vigilant team that is prepared to educate and convince hospital staff that nosocomial infection is important and that its impact can be lessened by application of effective methods.

In India we need to establish registry of the nosocomial infection. To begin with this could be started from very well known NICUs and ICUs of big cities. Infectious Diseases Chapter should take the lead for such a work.

Management

1. **Pneumonia:** Management of suspected bacterial nosocomial pneumonia depends on both patient and hospital related considerations, while awaiting culture results.

   - The choice of initial antimicrobial therapy depends on
   - Patient's underlying disease
   - Previous antimicrobial therapy
   - Neurological status (Seizures increase risk of aspiration)
   - Length of hospitalization
   - Gram stain results
   - Pathogens most likely to cause nosocomial pneumonia
   - Occurrence of viral and mycoplasma RTI in community
   - Antimicrobial susceptibility patterns of common pathogens based on microbiology surveillance data.
   - Treatment of nosocomial pneumonia in mechanically ventilated patients[10], comprises of two drug regimens with the potential for synergistic action against P.aeruginosa.
   - In suspected patient of nosocomial pneumonia in whom P.aeruginosa excluded, single antimicrobial may be appropriate. Otherwise, emergence of resistance and occurrence of superinfection has been reported with single drug therapy
   - For single drug therapy:
   - Ceftazidime: inferior activity against anaerobic organisms and S.aureus
   - Imipenem-cilastatin: good activity against all major bacteria causing nosocomial pneumonia.
   - Ticarcillin-clavulanate: good for ICU patients
   - Penicillin, ampicillin or cefuroxime: in acute aspiration or bacterial super infection of viral disease in immunocompetent, nonintubated child.
   - Ribavirin in treatment of RSV infection limited only to patients with
   - Underlying immunodeficiency
   - Chronic pulmonary disease
   - CHD(particularly those with pulmonary hypertension)
   - $PaO_2 < 65$ mm Hg. or increasing $PaCO_2$
   - Infants younger than 6 weeks (especially preterm)
   - Amphotericin B: Treatment of choice for invasive nosocomial respiratory infections caused by fungi, including aspergillosis and candidiasis. Although, now there are successful reports of treatment of aspergillosis with itraconazole and candidiasis with fluconazole, amphotericin B is still recommended.

2. **Surgical site infection:** Manage with all three antimicrobial agents + surgical intervention + nutritional support.

   - In pyogenic abscesses which are usually

due to clostridial myonecrosis and streptococcal gangrene, surgical intervention is the primary treatment modality with antimicrobials having secondary role.

- In postoperative infections in which the infected tissues are not devitalized, are well vascularized and are free from pressure, antimicrobial therapy is of paramount importance
- Infection from an abdominal or genitourinary tract operation requires polymicrobial coverage, including anaerobic bacteria coverage.
- In other surgical site infections, S.aureus is a likely pathogen, antimicrobial susceptibility patterns of S.aureus must be taken into account.

3. Infections associated with transfusion of blood and blood products:

- Empiric therapy started after appropriate cultures are obtained from recipient.
- For erythrocyte- associated infection, empiric therapy includes trimethoprim – sulfamethoxazole or an antipseudomonal coverage i.e. betalactam and aminoglycoside.
- For platelet-associated infection – penicillinase resistant penicillin and an aminoglycoside.

4. Nosocomial gastrointestinal infections:

- Rotavirus – An important cause of nosocomial infection in pediatric wards, detected in stools of symptomatic children.

  Treatment: Self limited, supportive therapy in the form of fluid and electrolyte balance.

Other, viruses causing nasocomial gastrointestinal infections are: adenovirus, Norwalk like virus, ECHO virus, calciviruses and astrovirus. Treatment is supportive in all these infections.

Antibiotic – associated diarrhoea (AAD):

- Common organisms are C.difficile and C.perfringens.
- Treated by discontinuing the antibiotic and providing supportive care.
- Patient with pseudomembranous colitis should be treated with antimicrobial therapy.
- Oral metronidazole, bacitracin, vancomycin are effective in eradicating C. difficile.
- In vancomycin – resistant enterococci, metronidazole is the first line treatment
- Bacitracin and vancomycin should be reserved for patients who do not respond to metronidazole.
- Administration of Lactobacillus may help to restore normal flora.
- Treatment response is generally within 24 to 48 hours, diarrhea and other symptoms usually resolve within 5 days.
- Nosocomial transmission of C.difficile most commonly results from person to person transmission after inadequate hand washing by health care workers.

Necrotizing enterocolitis:

- Oral feeding discontinued
- Gastrointestinal decompression via suction
- Empiric broad-spectrum parenteral antimicrobials (ampicillin or vancomycin and an aminoglycoside); Clindamycin for anaerobic coverage

- Surgery reserved for intestinal perforation or those who deteriorate despite aggressive medical therapy.

Points to remember

- Controlling nosocomial infection is of very major importance and must extend into many facets of pediatric hospitals and intensive care setups.
- Infection control team should educate and convince staff that nosocomial infection can be reduced to a greater extent by application of effective methods.
- Management of nosocomial infection should depend on patient specific as well as hospital related considerations, based on microbiological surveillance data.

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NEWS AND NOTES

2nd ANNUAL PEDIATRIC PULMONOLOGY UPDATE
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IAP HOWRAH DISTRICT BRANCH

Date: 2nd November 2003, Sunday **Time**: 9am – 5pm.
Venue: Auditorium, Ramkrishna Mission Seva Pratisthan, 99, Sarat Bose Road, Kolkata.
Faculty: Dr.G.S.Sethi, MAMC New Delhi.
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INFECTIOUS DISEASES

NEWER CEPHALOSPORINS - WHEN AND HOW?

** Niranjan Shendurnikar*
*** Mukesh Kumar Singh*

Abstract: *The new fourth-generation molecules and orallyactive agents are valuable additions to the cephalosporin family of antibiotics. Cefepime is a first-line agent for Enterobacter infections and may also be used in complicated urinary tract infections. It is also an effective agent to treat meningitis caused by common pathogens as is cefpirome. These two antibiotics are as active as ceftazidime against Pseudomonas. For community-acquired upper respiratory infections, cefdinir or cefpodoxime may be used orally. Oral cefixime can be used to treat urinary tract infections conveniently.*

The discussion also includes relevant information about these drugs' spectrum of antibacterial activity, pharmaco-kinetics, dosages, drug-interactions and adverse effects and provides guidelines for their clinical indications. The risk of emergence of resistant strains with their injudicious use should guide clinicians to restrict their use to standard indications.

Key words: *Fourth generation cephalosporins, oral antibiotics, meningitis, pneumonia, UTI.*

The mold Cephalosporium acremonium was isolated from sewage outflow in 1945 and was found to produce substances that inhibited both gram-negative and gram-positive bacteria[1]. Dozens of modifications have since been made to the parent compound, improving antimicrobial activity and creating an entire family of semi-synthetic antibiotics.

Unfortunately, these agents also have become some of the most widely misused medications available today, resulting in the emergence of multi-drug-resistance in many pathogens. Multiple mechanisms of resistance have developed to the older cephalosporins, especially by organisms, which inherently have inducible beta-lactamases that are active against even the third-generation agents (e.g., Enterobacter cloacae, Citrobacter freundii and Pseudomonas)[2]. Antibiotic resistance among hospital-acquired gram-negative bacteria has been a long-term and well-recognized problem; resistance has been observed in multiple genera, including Escherichia, Enterobacter, Klebsiella, Proteus, Salmonella, Serratia and Pseudomonas spp. Of even greater concern is the more recent development of gram-negative bacilli carrying extended-spectrum beta-lactamases. These enzymes were first detected in the mid-1980s in Western Europe and they have become increasingly prevalent. Most such strains are resistant to all beta-lactam antibiotics except cephamycins and carbapenems[3].

With increasing drug resistance, other factors too contribute to the need for new antibacterial agents. In this era of managed care, efforts are being made to decrease hospital admissions and cost of treatment. New oral antibiotics with improved absorption could replace intravenous infusion of certain antibiotics

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and obviate the need for admission in some patients. Many of the newer antibiotics offer once-daily dosing, increasing patient compliance and decreasing outpatient treatment failures. Adding to the antibiotic armamentarium also improves the choices available for patients with multiple drug allergies and for those in whom drug interactions are of concern[4].

Owing to the diversity of the class, no ideal system for the classification of the cephalosporins has been developed. The system most commonly used is one that combines parenteral and oral cephalosporins into "generations" based loosely on their spectrum of activity. Within any generation, however, individual antibiotics may have marked differences in microbiologic activity and other pharmacologic properties[1].

Of the third-generation molecules, cefotaxime and ceftriaxone have been widely used in the treatment of pediatric infections for more than a decade now. Ceftazidime is an effective anti-pseudomonal cephalosporin, cefoperazone being the hitherto available alternative, although with weaker activity. It should be noted that only ceftriaxone, cefotaxime and ceftazidime reach levels in the cerebrospinal fluid sufficient to treat infections of the central nervous system reliably[1].

Newer cephalosporins

The following discussion focuses on the basic properties of the fourth-generation cephalosporin antibiotics as a class, with an emphasis given to their unique properties and indications; the oral third-generation cephalosporins are also discussed.

The fourth-generation cephalosporins

The fourth-generation agents are dipolar ionic compounds, compared with the anionic third-generation agents. The newer agents diffuse more rapidly into gram-negative bacteria and they also have a lower affinity for beta-lactamases in the periplasmic space of gram-negative organisms. In vitro, these agents seem to be poor inducers of beta-lactamases, which is hoped to correlate clinically with a lower rate of development of resistance among gram-negative organisms[2].

The fourth-generation agents maintain broad antimicrobial activity against the Enterobacteriaceae, surpassing that of the third-generation agents. They maintain excellent activity against H. influenzae, N. gonorrheae and N. meningitidis. These agents are as active as ceftazidime for P. aeruginosa, and perhaps more active for Acinetobacter[2]. Table 1 shows the relative efficacy of some of the newer antibiotics against common pathogens.

Cefepime

Cefepime, the first of the"fourth-generation" parenteral cephalosporins, has excellent gram-negative coverage, while maintaining good gram-positive activity comparable to the second-generation cephalosporins. It lacks activity against Enterococcus spp. and has very poor activity against methicillin-resistant species of S. aureus (MRSA), Staphylococcus epidermidis and coagulase-negative Staphylococcus spp. Its antipseudomonal activity is comparable to that of ceftazidime. Cefepime's major advantage over the third-generation cephalosporins is its increased activity against Enterobacter cloacae and ceftazidime-resistant E. cloacae, organisms frequently identified in hospitalized patients[4]. Cefepime, imipenem-cilastatin and meropenem, unlike ceftazidime, have excellent activity against streptococcus viridans and pneumococci.

Cefepime has excellent CSF penetration in children with meningitis but is not yet approved by the United States FDA for this indication[4]. Thus, cefepime should be reserved for the treatment of multidrug-resistant gram-negative organisms, preferably with documentation of

Table 1. Antimicrobial spectrum of newer cephalosporins

Antibiotics/Organisms	Cefdinir	Ceftibuten	Cefepime	Cefpirome
Respiratory Pathogens				
S. pneumoniae	++	-	++	++
PCNR SP	-	-		+
MR SP		-		
S. aureus	++	-	-	+
PCNR SA	+			
MR SA		-	-	-
MR CR SA		-		
H. influenzae	++	++	++	++
K. pneumoniae	+-++	++	++	++
Moraxella	+-++	+	+	
Serratia	-	+	++	+
P. aeruginosa	-	-	+	+
Urinary Pathogens				
E. faecalis	-	-		
E. faecium		-	-	-
VREF		-	-	-
E. coli	+-++	++	++	++
Proteus mirabilis	++	++	++	++
Proteus vulgaris	-	++	++	+
Sexually Transmitted Diseases				
N. gonorrheae	++	++	++	
Other Gram-Positive Organisms				
Coag. neg. staphylococcus	+	-		+/-
MR CNS	-		-	
S. pyogenes	++	+-++		
Group A Streptococcus		++	++	++
Group B Streptococcus		-	++	++
N. meningitidis		++		
S. viridans	+/-	-		
Other Gram-Negative Organisms				
Shigella	++	++		
Salmonella	++	++		
Enterobacter spp.	-	-	++	+

++ 90% of organisms were sensitive. + 75%-89% of organisms were sensitive.

+/- 60%-74% of organisms were sensitive. - Less than 59% of organisms were sensitive.

PCNR, Penicillin resistant; SP, S. pneumoniae; MR, Methicillin-resistant; SA, S. aureus;CR, Ciprofloxacin-resistant; VREF, vancomycin-resistant Enterococcus faecium; CNS, (coag. neg. staph), coagulase-negative staphylococci

drug resistance. It should be considered a first-line agent in Enterobacter infections because resistance to the third-generation cephalosporins is well documented. It can also be used as one of the agents to provide double coverage in suspected pseudomonal infections.

Cefepime has been shown to be as effective as cefotaxime in the treatment of meningitis caused by H. influenzae (type b), N. meningitidis and S. pneumoniae in infants. The manufacturer-recommended dose is 50 mg/kg q8h for pediatric meningitis[4]. It is an alternative to ceftriaxone and cefotaxime in the treatment of E.coli meningitis[5].

Cefepime has been used in a variety of infections including uncomplicated and complicated urinary tract infections, skin and soft-tissue infections and pneumonia[1]. It should be reserved for the treatment of serious infections, especially those in immunocompromised patients and polymicrobial infections. Indications for its use include the empiric treatment of febrile neutropenic patients (dose enhanced to 50 mg/kg q8h), abdominal sepsis (with metronidazole), meningitis, Pseudomonas infections in cystic fibrosis patients, complicated UTI's and pneumonia[4].

In two multicenter, randomized trials, cefepime (50 mg/kg/dose every 8 h and every 12 h) was compared with ceftazidime (50 mg/kg/dose every 8 h) for the treatment of serious urinary tract infections including pyelonephritis in children less than 12 years of age. In these studies, a favorable clinical and microbiologic response was observed in >95% of ceftazidime-treated and cefepime-treated children assessed at the end of treatment[6]. The recommended dose is 100-150 mg/kg/24h, IV/IM, q8-12h. Cefepime may be used in the presence of mild renal dysfunctiðn without dose modification and for patients being treated with nephrotoxic drugs, such as cisplatin, cyclosporin or amphotericin B. The dose should be adjusted in patients with renal impairment or patients on either continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis[1].

There is complete cross-resistance between ceftazidime and cefepime, whereas both are usually active against aminoglycoside-resistant P. aeruginosa strains. All antipseudomonal cephalosporins when combined with aminoglycosides and particularly with amikacin are synergistic in vitro. Even for strains highly resistant to both compounds, an enhanced bactericidal effect with in vivo relevance has been described[7]. Similarly, a third or fourth generation cephalosporin in combination with an aminoglycoside is used to treat Citrobacter spp. sepsis or meningitis[5]. Cefepime has been used safely in infants and children.

Cefpirome

Cefpirome is a new intravenous and intramuscular fourth-generation cephalosporin with a bullet-shaped zwitterionic structure that enables it to penetrate rapidly into the periplasmic space of bacterial cells. It binds with high affinity to specific penicillin-binding proteins (PBP's) to exert its bactericidal effect[2]. It has good activity against Enterobacteriaceae, which display significant resistance to the third-generation cephalosporins. It is beta-lactamase resistant and has activity equal to ceftazidime against P. aeruginosa and equal to or better than ceftazidime and cefotaxime against staphylococci, streptococci, H. influenzae[4]. It has moderate but useful activity against enterococci, esp. Enterococcus faecalis. Cefpirome has a slightly better gram-positive activity than does cefepime[2].

Cefpirome is highly active against common pathogens involved in pediatric meningitis, including S. pneumoniae, H. influenzae and E. coli. It is twice as active as ceftriaxone and cefotaxime against penicillin-resistant S. pneumoniae, which is becoming an increasingly important pathogen. A dose of 50 mg/kg given

IV results in CSF concentrations well above the MIC_{90} of S. pneumoniae at 2, 4 and 8 hours after administration. Cefpirome is not currently approved for the treatment of meningitis by US-FDA but has excellent potential for this indication in the future. Cefpirome is safe for use in neonates and children[4].

Cefoperazone – Sulbactam

Cefoperazone became commercially available in early 1994. A Post-Marketing Surveillance Study in hospitalized pediatric patients found that over 90% of children with pneumonia responded to cefoperazone monotherapy[8].

Cefoperazone/sulbactam is the only synergistic combination of a cephalosporin with a beta-lactamase inhibitor and has become available recently. Sulbactam is active against the beta-lactamases of Haemophilus, M.catarrhalis, many Enterobacteriaceae, B.fragilis and S.aureus, but not against that of more resistant gram-negative organisms including Pseudomonas, Enterobacter and Citrobacter[2]. Unlike with other cephalosporins, no adjustment in dosage for cefoperazone is required in the presence of renal impairment. It may be used for empiric therapy of severe infections, when the causative organisms are suspected to be resistant. It is effective against most Gram-positive and Gram-negative aerobes (including Pseudomonas and Acinetobacter) and anaerobes, thus useful for mixed infections. Cefoperazone can cause a disulfiram (antabuse)-like effect, so patients should avoid alcohol-containing medications, e.g. elixirs for upto several days after therapy[2].

New Oral Cephalosporins

As a class, the oral cephalosporins have the advantage over oral penicillins because of somewhat better safety profile and greater palatability of the suspension formulations[5]. The third-generation oral cephalosporins include cefixime, ceftibuten and cefpodoxime proxetil with cefdinir, a recent addition, besides the new oral second-generation agent cefprozil.

Like cefaclor and cefuroxime, cefixime, cefpodoxime, ceftibuten, cefprozil and cefdinir have the advantage of adding H.influenzae (including beta-lactamase-producing strains) to the spectrum of cephalexin. Cefixime and ceftibuten have the limitation of having less activity than the others against pneumococcus, particularly against the penicillin resistant strains[2].

Cefdinir

Cefdinir has excellent activity against S. aureus (including penicillin-resistant S. aureus) while maintaining good gram-negative coverage. It is not useful in infections caused by Pseudomonas aeruginosa or Bacteroides spp. but is similar to cefixime and superior to cefuroxime against the Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae, Citrobacter diversens, Proteus mirabilis, Salmonella spp., Shigella spp., Aeromonas and Yersinia spp.)[4]. A 10-day regimen of cefdinir 14 mg/kg OD or 7 mg/kg BID was as clinically effective overall as a 10-day regimen of amoxicillin/ clavulanate 40/10 mg/kg/day divided TID in the treatment of tympanocentesis-confirmed, nonrefractory AOM in children[9]. Cefdinir, cefprozil, cefpodoxime and cefuroxime offer better activity than amoxicillin against beta-lactamase-positive H.influenzae and Moraxella[2]. Cefdinir may be used in acute sinusitis, community-acquired pneumonia, acute otitis media and skin and soft tissue infections[4].

Cefdinir can lead to antibiotic-associated colitis. Iron supplements, multivitamins and antacids containing magnesium or aluminium interfere with its absorption, thus necessitating dosing intervals[4]. Cross-hypersensitivity among the beta-lactam antibiotics has been clearly documented, so caution should be exercised if

cefdinir is to be given to penicillin-sensitive patients.

Ceftibuten

Ceftibuten is a new orally available third-generation cephalosporin. It has excellent activity against group A streptococci, Neisseria meningitidis, Neisseria gonorrheae, and Haemophilus influenzae, including beta-lactamase-producing strains, moderate activity against Moraxella catarrhalis, and weak activity against Streptococcus pneumoniae and Staphylococcus spp. It has a broad gram-negative spectrum, including E. coli, Salmonella, Shigella, and Yersinia spp. Resistant species include Enterococcus and Pseudomonas spp. and gram-negative anaerobes. Ceftibuten is US-FDA approved for the treatment of acute otitis media (AOM), Group A streptococcal (GAS) pharyngitis and tonsillitis. Dosages are 400 mg/day for adults and 9 mg/kg/day in children[4].

Ceftibuten is US FDA approved for the treatment of AOM secondary to H. influenzae, M. catarrhalis and S. pyogenes, but not S. pneumoniae. Because S. pneumoniae is a pathogen in approximately 7% of these infections, ceftibuten should not be considered first-line therapy. In clinical trials, ceftibuten showed a 93% clinical cure rate compared with 97% with amoxicillin/clavulanate (P = 0.10). Amoxicillin is still considered first-line treatment for AOM, but once-daily ceftibuten should be considered for patients in whom compliance is an issue and in those who are allergic to the penicillins but tolerate the cephalosporins[4].

A 10-day course of ceftibuten (9 mg/kg/day) resulted in a better overall clinical success rate than penicillin V in the treatment of GAS pharyngitis (97% vs. 89% respectively; $P < 0.01$)[4]. No data are available on its effectiveness in the prevention of rheumatic fever. Ceftibuten is a well-tolerated antibiotic. Diarrhea is the most common side effect, occurring in 3% to 9% of patients. There is a lower rate of diaper dermatitis in the pediatric population as compared with amoxicillin/clavulanate (17% vs. 3%), which could be secondary to the decreased rate of diarrhea[4].

The antimicrobial spectrum of ceftibuten is thus limited to streptococci, Hemophilus influenzae and most Enterobacteriaceae, with no appreciable anaerobic activity. It is effective for the treatment of lower respiratory-tract infections (if penicillin-resistant S. pneumoniae is not suspected), acute otitis media and pharyngitis and UTI[1]; however, in the treatment of these conditions, ceftibuten provides no significant advantage over older less expensive drugs. It may be used as follow-up oral therapy for patients who have been on IV cephalosporins. A small study found good clinical response to ceftibuten in enteric fever, with defervescence occuring in 3-5 days of therapy[10]. Once-a-day, oral therapy feasible at home is an obvious advantage.

Cefpodoxime proxetil

Being an esterified cephalosporin like cefuroxime axetil, cefpodoxime proxetil is not very palatable and its absorption is enhanced by administration with food[5]. It has somewhat less gram-negative activity in vitro than cefixime, but it has activity against S.aureus, absent from cefixime. Its pneumococcal activity is better than that of cefixime. In clinical practice, cefpodoxime, cefprozil and cefuroxime axetil can be used interchangeably for ambulatory treatment of community-acquired infections such as otitis media and sinusitis[2]. The dosage is 10 mg/kg/day, q12hrly. Chilling may help with compliance as the taste is bitter[5]. It may also be used for treatment of uncomplicated genital gonococcal infections.

Cefixime

Cefixime has excellent H.influenzae, B.catarrhalis and group A streptococcal activity

but is somewhat less active against S.pneumoniae than the second-generation agents. It has no activity against S.aureus.

Oral cefixime can be recommended as a safe and effective treatment for children with fever and urinary tract infection[11]. Despite its higher cost, use of cefixime will result in substantial reduction of health care expenditure as it avoids the cumulative costs of treatment failures. Studies have proved the efficacy of oral cephalosporins (e.g., cefixime, cefpodoxime or cefprozil) with a preceding dose of intramuscular ceftriaxone (50 mg/kg/dose). Hoberman and colleagues reported that patients given a single 16-mg/kg/day dose, then an 8-mg/kg/dose b.i.d. for 10 days did not suffer renal scarring at a higher rate than those children treated with parenteral antibiotics[11]. A comparative trial of the efficacy of oral cefixime vs. initial (first 2 days) intramuscular ceftizoxime followed by cefixime for the treatment of UTI in children found comparable cure-rates in both group[12].

More than 90% of UTI's in children under 2 years of age are caused by E.coli. Oral second-generation and third-generation cephalosporins are advantageous in that they are also likely to be effective against Proteus mirabilis and Klebsiella pneumoniae—organisms that account for most of the remaining cases of community-acquired childhood UTIs[3]. Following treatment of UTI, prophylaxis with cefixime (4 mg/kg, once daily) for 2 weeks [until a voiding cystourethrogram (VCUG) was performed] has also been reported[11].

Cefixime (20 mg/kg/day in two divided doses) for 7 days may provide a useful alternative treatment in cases of uncomplicated enteric fever in children, but it is less effective than short course treatment with ofloxacin[13].The current Centers for Disease Control (CDC) recommendations for the treatment of uncomplicated infections with Neisseria gonorrhoeae include ceftriaxone, 125 mg IM, or cefixime, 400 mg orally as a single dose[1]. Among febrile neutropenic children who are at low risk for complications, studies show that a change after 48–72 h of intravenous antibiotics to oral cefixime alone provides therapy that is as effective and safe as continuation of intravenous antibiotics, if a favorable clinical response is observed with initial IV therapy[14].

Adverse effects of newer cephalosporins

Adverse effects are similar to those induced by other cephalosporins (i.e., hyperpersensitivity reactions, eosinophilia, neutropenia, positive Coombs' test without hemolysis, and mild reversible elevations in liver enzymes). All have some effect on fecal flora with overgrowth of enterococci and yeasts and sometimes of Clostridium difficile (antibiotic-associated colitis).

Cefoperazone in particular, because it is excreted mainly through the bile into the gut, causes major changes in fecal flora, and diarrhea is more common than after other parenteral cephalosporins. Because cefoperazone has a *N*-methylthiotetrazole side-chain, it may cause hypoprothrombinemia and bleeding. The commonest adverse effect of oral therapy is diarrhea.

Epilogue

It is important to remember that new drugs need not necessarily be equal or better. The fourth generation agents should be used judiciously in settings where resistant infections are likely, e.g. nosocomially acquired infections especialy in a critical care unit, or empiric therapy for fever in neutropenic patients. The new oral agents must also be used only as second-line therapy, as they exert high selection pressure on bacterial populations for emergence of resistant strains owing to their broad spectrum of activity. Hence time-tested antibiotics with a narrower spectrum

and lower cost should always be the drugs of choice. The newer agents should not be routinely used to treat community-acquired infections but may be used for treatment failures, relapse following conventional therapy or in situations where compliance is an issue. They have a role as follow-up agents to complete a course of antimicrobial therapy initiated using parenteral agents.

Points to remember

- Newer cephalosporins maintain broad anti microbial activity against pathogens such as H. influenzae, N.meningitides and P. aeruginosa.
- Many of these agents offer improved pharmacokinetics and a convenient dosing schedule.
- These agents are useful addition for the treatment of infections such as those in immunocompromised patients, polymicrobial and /or serious infections.
- These agents are suitable alternatives for the treatment of complicated UTIs and severe pneumonia.

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INFECTIOUS DISEASES

PNEUMONIA IN CHILDREN - TREATMENT STRATEGIES

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Abstract : *Pneumonia accounts for high morbidity and mortality in children. Early diagnosis and prompt treatment is the key to successful outcome. Diagnostic and treatment strategies vary at each level of health facility and must be adopted to maximise cost effectiveness. At primary community level, child with cough in presence of tachypnoea is considered as pneumonia and treated with oral cotrimoxazole, a drug which is safe, effective, cheap, easy to administer and devoid of side effects. Sole aim in the treatment of pneumonia in the community is to prevent morbidity and mortality even at the cost of over-treatment. In office practice, individual patient may be diagnosed accurately with appropriate investigations and treated with specific antibiotic. Guidelines for treatment of pneumonia must be followed in general though modified to suit individual situations if necessary.*
Key words : *Pneumonia, treatment strategies, guidelines.*

Pneumonia is a leading cause of mortality in children worldwide. WHO has proposed a mortality burden of 2.6 million childhood deaths annually attributable to acute respiratory infection[1]. It is estimated that in India, 94 out of 1000 children below 5 years of age develop pneumonia annually, accounting for 20-25% of hospital admissions. About 12% of deaths in infants and preschool children are attributed to pneumonia, most of them being bacterial in origin[2]. With such a magnitude, it is necessary to plan modalities that would reduce mortality and morbidity due to pneumonia. Treatment strategies for pneumonia should take into consideration problems that are peculiar to our country. Socioeconomic and literacy status of the community, prevailing KAP (Knowledge, Attitude and Practice), non-availability of medical facilities for proper diagnosis and treatment, varying expertise of health care providers and poor standardization of protocols for treatment are hurdles in the ultimate reduction of mortality and morbidity due to pneumonia. Early clinical diagnosis and timely specific treatment is the key to successful outcome of pneumonia.

Treatment strategies for pneumonia would essentially vary depending upon the target population. Community acquired pneumonia in a location where no medical facilities exist poses different challenge than that occurring in well-established medical centre with trained doctors and modern facilities for proper diagnosis. Basic aim of treatment "where there is no doctor" is to reduce mortality based on simple algorithm even at the cost of overdiagnosis whereas in a medical facility, therapy is tailored to achieve maximum individual benefit. Naturally, treatment protocols for general community will have to be formulated to minimize mortality and the same may not be ideal for an individual patient. Pneumonia due to nosocomial infection is a special problem that is faced by critical care units and treatment strategies differ widely depending upon bacteriological profile and drug sensitivity pattern. Pneumonia in an immunocompromised

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host is a selective problem for special therapeutic consideration. Recurrent or persistent pneumonia needs proper investigations for ideal therapy.

We live in an era when medical practice is increasingly regulated by guidelines and protocols. Ideally, such guidance should be evidence based and in particular it is generally recommended that advice on medical treatment should be based on the results of adequately powered, double blind, placebo controlled trials or, some would say, better still, a meta-analysis of several such trials. Unfortunately evidence of such a high standard is often lacking. However, guidelines can be formulated useful for application to the majority of the children in the community. Such guidelines may have to be modified suitably from time to time in each country depending upon local observations.

Diagnosis of pneumonia and judging its severity

Prerequisite to treatment strategies is proper diagnosis of pneumonia and judging its severity. It is only then that guidelines can be formulated for general application.

Application in the community: Cough is the baseline symptom of acute respiratory infection and hence any child presenting with cough is a probable candidate for presence of pneumonia. Strategies for treatment of pneumonia in the community have been standardized by WHO and are followed in our country[3]. These guidelines are based on studies of clinical features of pneumonia observed in children, to determine the signs that are most reliable for use by relatively untrained health workers. In these studies, tachypnoea has been a consistently useful sign of pneumonia. The guidelines therefore emphasise the importance of tachypnoea in the diagnosis of childhood pneumonia, defined according to the WHO criteria: In children <2 months: >60 breaths/minute, in children 2-12 months: >50 breaths/minute and in children >12 months: >40 breaths/minute. Absence of tachypnoea is considered against the diagnosis of pneumonia.

Moreover, the severity of the tachypnoea is related to the severity of the illness, although pneumonia can occur in the absence of tachypnoea rarely. Severity of pneumonia is easily judged by presence of chest indrawing. As pneumonia worsens, child comes with danger signs- the child may stop feeding or sucking, has grunting during respiration, may develop drowsiness, convulsions, cyanosis, apnoea, abdominal distension and hypo or hyperthermia. Based on these simple clinical features, health worker or even the mother can make a presumptive diagnosis of pneumonia. So every child presenting with cough is classified on the basis of above-mentioned signs as Cough without tachypnoea = No pneumonia; Cough with tachypnoea = Pneumonia; Cough with tachypnoea with chest indrawing = severe pneumonia and Cough with tachypnoea with chest indrawing with danger signs = very severe pneumonia. Such classification is necessary to consider standard treatment for each class of patients in the community in children beyond 2 months of age.

In infants <2 months of age, every pneumonia is considered to be severe pneumonia and treated accordingly. It is important to realize that cough is not a feature of pneumonia in a young infant and this fact poses problems for health worker or mother to diagnose pneumonia.

Application in office practice: In office or institution practice, diagnosis of pneumonia may be considered by detailed analysis of clinical symptoms and physical signs supported by radiological and laboratory investigations. However, it is mandatory to follow simple guidelines useful for the community, mentioned

above. Modified guidelines useful for small hospitals have been developed by WHO[4]. Relevant physical signs and investigations can further supplement such simple primary observations. Classical physical signs of pneumonia include diminished chest movements on affected side, impaired note on percussion and bronchial breath sounds with crepitations. However, auscultatory signs have rather lower specificity and much poorer reproducibility between observers. Thus even in office practice, clue to diagnosis of pneumonia comes from simple observations useful for health worker or mother, which can be further confirmed by physical examination. Pneumonia is the clinical diagnosis and hence physical examination does not suggest etiology.

Laboratory investigations for defining etiology: Most of the laboratory tests fall short of precise etiological diagnosis. Unlike common belief, neutrophilic leucocytosis is seen in both bacterial and viral pneumonia though marked changes may favor bacterial etiology. The results of acute phase reactants (C reactive protein, erythrocyte sedimentation rate) are widely distributed in both bacterial and viral pneumonia and cannot be relied on for etiological diagnosis. In the absence of sputum culture, indirect methods of identifying causal bacteria lack both sensitivity and specificity. Nasopharyngeal bacterial culture is useless, but upper respiratory tract secretions are useful in virological diagnosis. Bacterial serological tests are unreliable, with the exception of paired Mycoplasma pneumoniae titres, although the necessary delay in performing these tests reduces their usefulness in guiding treatment. Thus even with adequate laboratory facilities, etiological diagnosis is difficult and guidelines become necessary to apply. The best guide for distinguishing bacterial and viral pneumonia is clinical acumen, and the guidelines present two well-validated clinical observations that should reduce inappropriate antibiotic use in toddlers, while identifying those children who do need antibiotics[5]:

- In the preschool child, if wheeze is present, primary bacterial pneumonia is unlikely
- Bacterial pneumonia tends to be associated with pyrexia, dyspnoea and tachypnoea; should be considered in children up to 3 years of age with a temperature >38.5°C along with chest recession and respiratory rate >50 per minute.

Radiological diagnosis: Radiological signs of pneumonia overlap with those of collapse, but airbronchogram depicts radiological consolidation and does suggest a bacterial cause.

Etiology of pneumonia may be guessed to some extent on the basis of radiological characteristics. Lobar consolidation in older child is suggestive of pneumococcal pneumonia. Lobar consolidation with pleural effusion may be taken as Haemophilus infection while broncho-pneumonia with pleural effusion may suggest possibility of streptococcal disease. Breaking down necrotising pneumonia is a feature of either staphylococcal or klebsiella pneumonia. Pneumonia with mediastinal lymphadenopathy is likely to be tuberculous pneumonia. Nevertheless, there is good evidence that chest radiography has no effect on the outcome of the illness. The case for performing a chest *x* ray as part of the investigations of a febrile child with no respiratory signs is dubious, except in an young infant. If clinical signs are present, *x*- ray examination is not necessary to diagnose pneumonia. In children in whom clinical recovery has been satisfactory, repeat *x*- ray examination serves no useful purpose. It is clear that while diagnosis of pneumonia may be partly facilitated by medical facilities, guidelines suitable for general community are also very useful for clinicians.

Treatment strategies

For community guidelines: In the absence of pneumonia, child needs merely supportive therapy without antibiotic. Supportive treatment includes breast-feeding or good nutrition, hydration and general hygienic measures. Paracetamol is preferred drug for symptomatic therapy for fever. Cough mixtures are not useful except in presence of wheezing wherein bronchodilator may be effective.

Child with pneumonia must be treated with oral antibiotic. Choice of antibiotic for the community use is obviously limited and based on knowledge of common etiological agents causing pneumonia. Such an antibiotic must be cheap, safe, devoid of any significant side effects, easy to administer in term of correct dose and of course fairly effective. Co-trimoxazole is considered to be the best even for use by health workers or mothers without medical guidance. As discussed above, main aim of treatment of pneumonia in the community is to reduce mortality and hence few shortcomings of co-trimoxazole need to be ignored in favour of larger benefits. This is not an ideal drug for every organism causing pneumonia but may be a drug that is likely to act against most of the bacteria. There are two problems that have emerged over years of experience of implementing this strategy. We are aware that with simple algorithmic approach to diagnosis of pneumonia in the community, children with wheeze and viral infections are likely to receive antibiotic without justification[6]. But such overuse of co-trimoxazole is a small price to pay for the benefit of reduction of mortality due to pneumonia and it may not be harmful. But the second problem refers to development of bacterial resistance to co-trimoxazole and hence search for an alternative drug[7]. Though bacterial resistance seems to be on the increase, it depends upon level of prevalence of such drug resistance. Most countries have reported drug resistance to the tune of 20-30 % and hence have continued with the policy of continuing use of co-trimoxazole in the community[8]. Amoxycillin may be another drug considered to replace co-trimoxazole but it is 3-4 times costly and has to be administered three times a day as against twice a day of co-trimoxazole. Clinical trials with short course Amoxycillin for 3 days have been found to be effective for non-severe pneumonia[9]. Other antibiotics are not considered for community use as they are either administered by parenteral route or oral but not cost effective. If pneumonia deteriorates into severe pneumonia, ideally referral to the hospital facility is essential. Only if referral is not possible or delayed, intramuscular antibiotic such as penicillin may be tried. Very severe pneumonia must be treated in a proper medical facility for successful outcome. In the community where diagnosis and treatment depends upon intervention by health worker or mother, it is essential to observe carefully and judge severity and follow standard strategy to reduce mortality risk.

For office practice: Treatment strategies in office practice may differ from that applied in general community simply because of availability of many alternative drugs and also offering tailored drug choice for individual patient. In children suffering from non-severe pneumonia, oral antibiotic may be adequate and the choice could depend upon local epidemiology. It is estimated that mycoplasma infection may account for pneumonia in about 30% of children[10]. Unlike in western countries, prevalence of mycoplasma pneumonia in India is high in children under 5 years of age and not restricted to older children. As macrolide is the preferred drug for such an infection, one may have to consider this drug for use in office practice. Unfortunately it is not possible to differentiate mycoplasma pneumonia from other bacterial infections clinically and thus choice of

antibiotic for non-severe pneumonia in office practice remains to be hypothetical largely based on experience of individual clinician. In case of severe pneumonia, hospitalization is necessary and standard protocols may be followed for these hospitalized patients. Benzyl Penicillin is the drug of choice and studies have shown good results in children hospitalized for severe pneumonia. In case of deterioration, chloramphenicol is the drug of choice and most of the bacterial strains are likely to be sensitive to this drug[11]. Only in case of very severe pneumonia especially with suspicion of staphylococcal or klebsiella infection, other antibiotics may have to be used in combination such as cloxacillin and gentamycin. Supportive therapy for severe pneumonia must include proper oxygenation and hydration. Very severe pneumonia may need mechanical ventilation and other monitoring facilities.

General care is important and attention must be paid to oxygenation, nutrition and hydration. Patients with pneumonia must be monitored carefully. Unnecessary interventions must also be avoided:

- Physiotherapy has no part to play in the management of community-acquired pneumonia.
- Young children presenting with mild symptoms of lower respiratory tract infection need not be treated with antibiotics
- Antibiotics administered orally are safe and effective for children presenting with community acquired pneumonia
- Intravenous antibiotics should be used when the child is unable to retain oral antibiotics and in severe cases
- Amoxycillin is the first choice oral antibiotic for children <5 years
- Because mycoplasma pneumonia is also seen in young children, macrolide antibiotics may be used as first line empirical treatment in children even below aged 5 years and in case of failure to respond to primary drug of choice.

Nosocomial pneumonia: This is a special problem faced in critical care units. It is estimated that nosocomial infection may occur in about 5-10% of sick patients undergoing interventional monitoring even in the best units. This is because of impaired host defence of sick patients with access to infection through indwelling catheters or mechanical ventilation. In fact ventilated children are several times more likely to develop nosocomial pneumonia. Many of these sick children are also vulnerable to microaspiration of gastric contents, which leads to pneumonia. Standardised guidelines are difficult to develop for management of nosocomial pneumonia. It is mandatory to prove etiological agent responsible for pneumonia from secretions obtained by either endotracheal suction or bronchoscopic lavage. Broad spectrum antibiotics covering Gram+ve and Gram-ve bacterial infections must be instituted immediately and then changed according to drug sensitivity pattern. Early administration of suitable antibiotics is likely to save the child from further deterioration. Even with best of therapy, mortality is likely to be high in such patients.

Recurrent / persistent pneumonia: This condition demands proper evaluation based on individual assessment. It is mandatory to document complete reversal of pneumonia both clinically and radiologically in every patient because then only one can be sure of pneumonia being either recurrent or persistent. Treatment strategies would be decided by background cause of recurrence or persistence[12]. Persistent pneumonia is often due to improper choice of antibiotic or poor compliance of therapy. At

times, it may be a result of local malformation or retained foreign body. Recurrence could be either unilobar or multilobar and causes would vary accordingly. It is important to find the cause, as mere antibiotic therapy would not offer cure in such patients. Many times, asthmatic child may be wrongly diagnosed as pneumonia due to radiological shadows but clinical profile is different enough not to be confused.

Pneumonia in immunocompromised patient: Treatment strategies for such patients may differ only in terms of duration of therapy and not in the choice of antibiotic. Of course, such patients are more vulnerable to opportunistic infections such as tuberculosis, fungus or pneumocystis carinii and they need specific therapy for such infections.

Prevention is better than cure and hence ensuring preventive methods with the use of vaccines and other general measures must be emphasized. Besides routine immunization, use of recently available vaccines against Haemophilus influenza and pneumococcus need to be considered. It is known that Haemophilus influenza causes pneumonia in about 30% of children below 5 years of age thereby justifying routine vaccination at least in affordable population. There are not enough studies to recommend pneumococcal vaccine in routine practice as yet[13].

In summary, pneumonia accounts for high morbidity and mortality in children. Early diagnosis and prompt treatment is the key to successful outcome. Diagnostic and treatment strategies vary at each level of health facility and have to be adopted to maximise cost effectiveness. Guidelines must be followed in general though they may be modified to suit special situations if necessary.

Points to remember

1. Cough as a symptom and tachypnoea as a physical sign denotes pneumonia and should be treated with antibiotic even at primary community level. Presence of chest indrawing and other danger signs need referral to better health facility.

2. Etiological diagnosis and severity of pneumonia can be assessed by relevant laboratory tests and monitoring in secondary and tertiary level of health care and treated with specific antibiotics and other supportive measures as necessary.

3. Choice of antibiotic for community acquired pneumonia is wide and it is important to start any antibiotic at the earliest to prevent mortality and morbidity.

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NEWS AND NOTES

5TH NATIONAL CONGRESS ON PEDIATRIC CRITICAL CARE

Annual conference of Critical Care Subchapter of IAP is hosted by IAP, Surat branch, on October 10th, 11th & 12th, 2003 at Hotel Holiday Inn , Surat. Theme of the conference: 'Demystification of Critical Care'.

CME: October 10th, 2003. Conference: October 11th & 12th, 2003 Pre-Conference workshop / course,

a) PALS - 8th & 9th October b) Basic Pediatric Critical Care Course - 8th & 9th October

c) Workshop A - Advanced Mechanical Ventilation + All about Equipments - 9th October

d) Workshop B - Peritoneal Dialysis + IV access + All about Equipments - 9th October

Registration Details:

A) Conference:	**Till 30.04.03**	**Till 30.06.03**	**Till 15.09.03**	**Spot**
1. IAP Member	2000	2400	2800	3400
2. P. G. Student *	1600	2000	2400	2800
3. Non IAP Member	2200	2600	3000	3600
4. Associate Delegate	1250	1250	1500	1500
B) Workshop /Course	**Till 30.04.03**	**Till 30.06.03**	**Till 15.09.03**	
1 PALS	1200	1200	1200	No Spot
2 Basic Pediatric Critical Care course	2000	2250	2500	No Spot
For PG Student *	1500	1750	2000	No Spot
3 Workshop A	500	650	800	No Spot
4 Workshop B	500	650	800	No Spot

Note:- 1. Conference registration includes CME & Banquet.

2. Except PALS, registration for the conference is a prerequisite for participating in the workshops / basic course.
3. Limited participants to be taken for all the 4 workshops on 1st come 1st serve basis.
4. P.G. Students are required to attach certificate from the Head of the Department.
5. Registration not required for children below 12 years.

For children between age 5 & 12 years, lunch / dinner coupons available at reasonable rate.

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INFECTIOUS DISEASES

DENGUE ILLNESS : APPROACH TO CLINICAL DIAGNOSIS AND MANAGEMENT.

Ashok S. Kapse

At the end of the previous century, the world faced the resurgence of several infectious diseases, dengue being one of the most significant in terms of morbidity and mortality. The dengue virus is transmitted to man by the bite of domestic mosquito, Aedes aegypti being the prime vector although some other species such as Aedes albopictus also are of importance. Four viruses, dengue-1 to 4, classified in an antigenic complex of the flavivirus genus, family flaviviridae, are the aetiological agents of this disease. Infection with one of these serotypes does not provide cross-protective immunity, so persons living in a dengue-endemic area can have four dengue infections during their life span. Over the last two hundred years dengue was known to the physician as a self limiting benign febrile condition[1]. However in the mid 1950 images of dengue illnesses underwent a drastic change. South East Asian countries experienced epidemics of a serious disease associated with dengue viruses. Patients afflicted from this new illness exhibited two potentially life threatening symptoms; bleeding diathesis and shock. Dengue hemorrhagic fever (DHF)-Dengue shock syndrome (DSS) was the new name coined for this entity[2]. Since then disease has spread to a large area of the world and is posing a progressively escalating public health problem in the tropics and sub tropics. Today 2·5 billion people live in dengue endemic area and disease is reported from over more than 100 countries. Though the true incidence is not very well known, yearly 50–100 million cases of dengue fever and few lakh cases of DHF are estimated to occur world wide[3]. In 1998, 1·2 million cases of dengue and DHF were reported to WHO, including 3442 deaths.

In spite of multiple dengue strain endemicity and countrywide invasion of Aedes aegypti, till very late India remained a silent zone [free of DHF][14]. However by late eighties this scenario started changing, beginning from Surat in 1988[15]. Sharp outbreaks of DHF have occurred all over the country. In the last decade many cities like Delhi, Kolkata, Bangalore, Chennai, Jaipur, Gwalior have suffered from DHF epidemic.

Two factors directly responsible for the burgeoning incidence of DF and DHF are proliferation in the density and geographic distribution of the vector, and marked increase in the rate and geographic range of virus transmission[2].

Major global demographic changes such as uncontrolled population growth, unplanned urbanization resulting in substandard housing, and need for water storage have greatly aided the vector proliferation. The increase in air travel allows the movement of the different serotypes, strains and even genotypes of virus from one region to another. Individuals in viremic phase are able to introduce a new virus into a vulnerable population. In general, factors that augment the contact between vector and host favour an increase in dengue transmission. However, climatic changes also influence virus evolution.

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WHO has reported that a temperature rise of 1–2° C could result in an increase in the population at risk by several hundred million, with 20,000–30,000 more fatal cases annually.

Pathophysiology

For years, DHF pathogenesis has been a matter of controversy. Some workers argued that secondary infection was the main factor in the severity of this disease, whereas others thought that viral virulence was of prime significance. Today, the majority view that secondary infection is the main risk factor for DHF; however, other factors such as viral virulence and host characteristics also have important bearings.

DHF occurs as an outcome of a very complex mechanism where virus, host, and host immune response interact to give the severe disease in 2–4% of individuals with secondary infection. Taking into account of the international experiences a basic hypothesis for the development of DHF epidemics was published in 1987[8]. The intersection of three groups of factors namely host, viral, and epidemiological factors determine the occurrence of a DHF epidemic. The epidemiological and viral factors are the determinants for an outbreak of the disease. Individual risk factors such as sex, race, and chronic diseases are the predisposing elements which determine the occurrence in a certain race or age group. However, the pre-existence of antibodies is the most vital individual risk factor.

First infection with any of the dengue virus in a non-immune individual results in self limiting febrile illness. Recovery from this first infection is accompanied by generation of immunological responses. Epitopes present on E protein are capable of inducing homologous as well heterologous neutralizing antibodies. Levels of these antibodies have a governing role in driving dengue infection to more or fewer infected cells. People infected with one serotype maintain a life-long protective immunity to infection by the homologous virus, although protective immunity to infection with heterologous serotypes is transitory. It has been proposed that neutralizing antibodies downregulate the severity of the disease. During a secondary infection with a different serotype, the presence of low amount of heterotypic neutralizing antibodies could prevent severe disease; on the other hand, when no neutralizing antibodies are present, heterotypic antibodies form complexes with dengue viruses, which infect mononuclear phagocytes with enhanced efficiency and as a consequence a higher number of cells are infected. This phenomenon has been called antibody dependent enhancement (ADE)[8]. Halstead et al in 1970 observed that DHF occurs in situations where more than one serotype circulate. Epidemiological and serological studies done in Thailand and Cuba firmly establish that secondary infection is a major risk factor for DHF.

Children are at higher risk of acquiring DHF than adults. Age-specific DHF incidence is observed to be bimodal, with severe cases peaking at 7months of age and again at 3–9 years of age. DHF or DSS occurred in infants almost exclusively during primary dengue infections. These infants were born to dengue immune mothers and had acquired maternal dengue antibody and subsequently experienced a dengue infection. On the other hand, children 3–5 years old have DHF during a secondary infection. Baseline microvascular permeability in children is supposed to be significantly greater than that of adults and this partly explains why DHF is more frequently observed in children[9,10].

There seems to be no time limit for sensitization after a primary dengue infection. The 1997 Cuban epidemic clearly demonstrated that dengue 2 DHF could occur even after 16–20

years of the primary dengue-1infection. Besides secondary infection, chronic diseases such as bronchial asthma and diabetes have been suggested as risk factors for DHF. Finally, whites have higher risk of developing DHF than blacks.

Neutralizing antibodies are key factors in the etiopathogenesis of the disease; however, the cellular immune response is also of immense significance. Recent observations suggest a massive T-cell activation due to interaction with infected monocytes and release of pathogenetic cytokines as a consequence of this interaction. Cytokines such as TNF [tumour necrosis factor], interferon, Interleukin-2 [IL], IL-6, IL-8, and IL-10 are found to be greatly elevated in DHF. High levels of TNF could be responsible in part for transient vascular damage. Recently a protein of 22–25 kDa has been detected in sera of DHF patients. This factor is able to induce increased capillary permeability in mice, and is capable of reproducing all the pathological lesions that are seen in human beings[11].

Several factors such as vasculopathy, prothrombin-complex deficiency, thrombocytopenia and platelet dysfunction are thought to be responsible for haemorrhage in DHF. However mechanism that initiates bleeding is yet to be established. Multiple factors such as high levels of platelet-activating factor inducing platelet consumption, virus-antibody complexes on the platelet surface and presence of cross reactive IgM antibodies, causing platelet lysis have been thought to be responsible for thrombocytopenia in DHF[3,11].

In spite of this knowledge, it is still uncertain what kind of host and virus-specified factors determine why certain individuals have only mild DF while others develop DHF. Viral strains, genotypes, mutants and sequence of infective strains are important contemplations. Dengue 2 genotype of Southeast Asian origin is found to be related to most of the DHF epidemics in Southeast Asia and the America. On the other hand the American genotype, is only related to DF epidemics in the American region. Recently, some amino acid changes on M and E proteins of dengue 2 strains have been found to be associated with DHF epidemics. The genetic variation between genotypes could be responsible for differences in virus interactions with macrophages and suggest that certain strains are more virulent than others. Morens and Halstead reported that subtle antigenic differences affect the degree to which strains form immune complexes with heterotypic antibodies[12,13].

Clinical features

Ranging from asymptomatic infection, to mild undifferentiated fever, to fatal shock, dengue illnesses have wide spectrum of clinical presentations. WHO identifies two types of illnesses, Dengue fever (DF) and Dengue hemorrhagic fever (DHF). Dengue shock syndrome (DSS) is a severe subset of DHF[3].
Dengue fever again presents in two ways: classical Dengue fever and undifferentiated febrile illness.

Classical dengue fever: Dengue in its classical form produces a characteristic clinical syndrome. After a short incubation period of two to seven days, there is an abrupt onset of high grade fever, which is associated with headache, retro-orbital pain, photophobia, backache, myalgia and arthralgia. For these symptoms Dengue has acquired an epithet of 'BREAKBONE FEVER'. Besides aches and pain, other common symptoms include extreme weakness, anorexia, constipation, altered taste sensations and colicky abdominal pain. A transient maculopapular rash may erupt on chest and back within the first few days of fever. Signs of skin bleeding such as positive tourniquet test, petechiae, or ecchymosis are observed in some patients. DF cases with

bleeding complications such as epistaxis, gingival bleeding, gastrointestinal bleeding, hematuria, and hyper menorrhea can be observed during some epidemics. Such phenomena tend to vary with different strains and with age and sex, in general bleeding manifestations being more severe in adults. Post-convalescence depression and bradycardia are also common in adults. Leucopenia and mild thrombocytopenia are two of the usually observed hematological changes. In majority of cases fever tends to last for three to seven days and terminates in an uneventful convalescence. However in few cases it tends to recur and hang about for few more days [saddleback fever].

Undifferentiated dengue fever : Unfortunately classical dengue fever is an uncommon presentation in pediatric age group. Majority of children present with undifferentiated febrile illness, posing lots of diagnostic problems. This undifferentiated dengue fever may present as fever with maculopapular rash and / or mild respiratory symptoms.

Dengue hemorrhagic fever: Plasma leakage is the major pathophysiological feature observed in DHF and differentiates this from typical DF. Initial clinical picture of DF and DHF are similar but the later part of the disease particularly peri and post defervescence period show marked differences.

In DHF defervescence coincides with intracellular viral killing (see pathophysiology) which in turn sets in process of vasculopathy making the capillaries leak. Extravasation of plasma, through these leaky capillaries result in hemoconcentration, hypovolemia and hypotension. In majority of cases leak is transient lasting for few hours and once it stops, patient quickly stabilizes and completely recovers. As with DF, convalescence in mild DHF is swift and uneventful.

In a small number of cases leak is prolific and prolonged, plasma may continue leaking for two to three days, fluid which leaks out manifests as generalized oedema and effusions in serous cavities. Untreated, such patients may develop severe shock. These cases are designated as DSS and carry bad prognosis. Only intensive and timely IV fluid therapy can salvage these patients. After couple of days, when leak is over, extravasated fluid returns to circulation. This sudden gush of fluid into circulation may cause circulatory congestion and sometimes even failure. Thus the course of the disease in DSS has three arbitrary phases; febrile, leaky and congestive[14].

Symptomatology of mild DHF (DHF without shock): Typically a case of DHF has three important findings: Fever, bleeding tendency and hepatomegaly. Commonest bleeding manifestation is positive tourniquet test. Bleeding at venepuncture site and fine petechiae scattered over trunk, axillae, face and palate, are usually observed. Epistaxis, gingival and mild GI bleed may occur infrequently. Less than 10% of Dengue hemorrhagic fever patients may have clinically frank and severe bleeding mainly from gastrointestinal tract.

Liver is usually palpable from early febrile phase, varies in size from 2-4 cms and is non tender. Anorexia, nausea, vomiting and vague generalized abdominal pain are common accompaniments.

Critical stage of the disease starts around defervescence which is often accompanied by circulatory disturbances as a result of plasma extravasations. Clinically patients manifest with; marked weakness, irritability, anxiety, restlessness, oliguria and giddiness. Majority of the patients stabilize at this point and recover completely within couple of days of defervescence[14].

Symptomatology of severe DHF (DHF/DSS):

Leaky phase : In a small number of patients capillary leak is profuse and continues for two to three days. These patients progressively become oliguric and exhibit signs of postural hypotension-like giddiness, inability to rise from recumbent position and need to be helped or carried for smallest movement. They have typical signs of circulatory failure: skin becomes cool, blotchy and congested and circumoral cyanosis is commonly observed. Untreated, these patients develop fast and thready pulse, imperceptible lower limb pulses (dorsalis pedis and posterior tibial), narrowed pulse pressure and in extreme cases unrecordable blood pressure. Severe right hypochondriac pain and progressive enlargement of liver coincides with the development of shock. These cases should be immediately hospitalized for intensive fluid therapy. Uncorrected shock heads for a complicated course and results in metabolic acidosis, DIVC resulting in severe bleeding and multi-organ failure. Poorly managed DSS patients have a high fatality rate of 30 to 40%. Besides signs of circulatory failure these patients also exhibit puffy and swollen face, generalized oedema and polyserositis[14].

Congestive phase: After two to three days, leak stops and plasma which had extravasated during the leaky phase, returns back to circulation causing vascular congestion. Now patients start passing copious amount of watery urine and develop bounding pulse, wide pulse pressure and rise in blood pressure. Few cases may develop frank congestive heart failure manifesting with tachycardia, tachypnoea, muffling of heart sounds and basal rales. This phase may continue for twelve to twenty four hours[14].

Convalescence: End of congestive phase heralds the recovery which, like in DF and DHF, is rapid and complete. Bradycardia, arrhythmias and characteristic confluent petechial rash are the signs seen during convalescence. Bright red confluent petechial rash erupts along the lateral margins of soles and palms, between eighth and tenth day of sickness. Rash shows tendency to lose confluence as it ascends up the limbs and to fade away above the knee and the elbow. In some cases there are small round areas of clear skin giving it a name of annular petechial rash[3].

Unusual manifestations: Liver failure and neurological involvement are recently described manifestations with dengue infections[6]. Patients with neurological manifestations are reported from India, Indonesia, Myanmar and Thailand. CNS expressions are in the form of convulsions, unconsciousness, spasticity and paresis. Till date there is no evidence for direct neurological involvement of brain by dengue virus.

Suspicion index: Serological studies demonstrate that dengue is endemic in our country, however excepting epidemic situations dengue is a rarely diagnosed condition. Want of a reliable suspicion index is the major reason for this anomaly. Working in a dengue endemic area for two decades the author has observed and tested a clinical finding which could reliably serve as a suspicion index for dengue illnesses, this suspicion index could be termed as **erythematous flush**.During their illness dengue patients develop a characteristic erythematous flush. Flush deepens with advancing disease and imparts peculiar facial features to these patients. Dengue facies could be portrayed as: suffused and swollen face, injected eyes, purplish lips and most importantly reddened malar region and ear lobes. In other words patients assume a measly look devoid of catarrh. Around eighty percent of patients suspected as dengue on the basis of this particular finding were proved to be viroserologically positive.

Lab investigations

1. Platelets and hematocrit: A rise in hematocrit and drop in platelets are the constant findings in

all cases of dengue hemorrhagic fever. These parameters exhibit a unique time-bound relationship with the disease. Changes start a little before the defervescence (4th or 5th day of sickness.) and peaks around the second or third afebrile day (7th or 8th day of sickness). Hemoconcentration and thrombocytopenia represent the pathophysiological hall mark of the disease viz, capillary permeability and abnormal hemostasis and bear a distinct correlation with the severity of the disease[4].

2. Serous effusions: Leaking plasma gets collected in serous cavities resulting in development of effusions. Peritoneum is the first and commonest site. In severe cases patients develop polyserositis [Peritoneal, pleural and pericardial effusions.] while a mild case may present with only ascites. Most marked on second to third post-defervescence day, these effusions resolve around tenth or eleventh day of disease and hardly ever need any therapeutic intervention[15].

3. Turk reaction cells: These are transformed lymphocytes. Presence of more than 20 percent of turk cells in buffy coat smear is a frequent finding for dengue hemorrhagic fever.

A typical plan for clinical diagnosis:

Patient presenting with fever and dengue facies [non catarrhal measly look] during or post monsoon season should raise the suspicion for dengue illness. A positive tourniquet test indicating bleeding tendency augments the possibility. Carry out CBC and platelet count serially, once during initial period and repeat around fourth to fifth day of fever. Patient showing rise in PCV and drop in platelets should be categorized as DHF. Keep this patient under close observation and monitor him for signs and symptoms of developing shock. Patient with absence of thrombocytopenia and hemoconcentration should be labeled as DF.

Management

Out patient management: Cases other than the DSS do not require hospitalization and could be managed at out patient level and the author suggests the following management-plan for such cases.

- Keep patient under close clinical observation for throughout the febrile period and two to three days beyond the defervescence.
- For pain and fever use only paracetamol, avoid aspirin and NSAID, as they interfere with platelet functioning.
- Give parents a set goal for child's fluid intake (100 to 150ml/Kg, bodyweight). Fluids could be water, ORS, milk, buttermilk, fruit juices etc.
- Instruct parents to collect child's urine and compare the output against fluid intake.
- Warn parents for bad clinical signs viz giddiness, restlessness, anxiety, severe abdominal pain and cold extremities.
- Carefully assess every patient exhibiting the above symptoms for signs of shock e.g. poor volume pulse, imperceptible pulses, narrowing of pulse pressure and fall in blood pressure. Patients with these symptoms need immediate hospitalization for intensive IV fluid therapy.
- Lastly one should bear in mind that DSS sets in with the defervescence, hence any child deteriorating or failing to improve with subsidence of fever should be carefully assessed for signs of shock.

Management of dengue shock syndrome

How to suspect DSS and when to hospitalize patients?: A patient of dengue illness showing the following signs and symptoms in peri defervescence period is likely to develop DSS.

monitoring. Obvious clinical bleeding, or severe internal bleeding as indicated by marked drop in PCV are indications for blood or packed RBC's infusion.

Indication for platelets: Main reasons for bleeding in DHF are vasculopathy and coagulopathy. Thrombocytopenia does contribute but in a minor way, therefore patients having thrombocytopenia in absence of obvious clinical bleeding, do not require platelet transfusion.

Use of vasopressors (Dopamine and Dobutamine): Though WHO does not recommend use of vasopressors the author has clinical experience for their recommendation.

Dobutamine: In severe cases myocardial engorgement occurs as a result of a poor cardiac contractility. Dobutamine, a drug with strong inotropic effect, is a useful remedy in such situations.

Management during congestive phase

How to recognize its onset?

After certain time varying between 12 to 72 hours, depending upon severity of case, DHF leak stops and fluid which had escaped out returns back to vascular compartment.

Following changes are likely to occur in monitoring criteria.

- Pulse: Pulse becomes fast and bounding.
- Blood pressure : Systolic pressure would go up and pulse pressure would become wider.[>50 mm of Hg]
- Abdominal girth starts decreasing.
- Intake/output ratio: The most important signal is narrowing gap between IV intakes and urinary output.

As the patient enters into congestive phase, change over to hypotonic fluid and decrease the rate to 3-5 ml/kg/hr. In the next few hours patient would pass copious amount of light colored urine.

In some patients regurgitant fluid may cause cardiac overload manifesting as cough, tachypnoea and tachycardia and such cases may need diuretics. Problem is infrequent and is likely to happen in patients treated with colloids. Congestive phase may end after 12 to 24 hours heralding recovery.

Reasons for mortality in DHF/DSS:

1. Failing to recognize that patient is in shock. It is the usual tendency of parents and treating physician to feel relieved when temperature subsides. However in dengue, patient may pass into shock with defervescence. Instead of a feeling of well being, display of anxiety, apprehension and giddiness at defervescence should immediately alert treating physician to the possibility of developing shock. Failure to appreciate this is the commonest cause of death in DSS.

2. Hemorrhages: Though dengue is known as hemorrhagic fever, clinical hemorrhages are uncommon and are rarely responsible for mortality. Shock effecting DIVC is the major cause for severe hemorrhages.

3. Failing to recognize that patient has entered congestive phase which may cause cardiac overload and consequent CHF and death.

Though a complex disease dengue hemorrhagic fever exhibits a set clinical pattern and observes a fixed time bound course of events. Awareness and familiarity with the disease and its course greatly facilitates diagnosis and initiating proper therapy. With appropriate IV fluid management and frequent monitoring, mortality in DSS should not exceed more than one percent[4].

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CONGRATULATIONS

* Dr.Uday Bodhankar standing committee member, International Pediatric association has the distinguished honor of being invited to participate in the 56th World Health Assembly scheduled in Geneva-Switzerland. He has been extended invitation by World Health Organisation through IPA and Common Wealth Association.

* Dr.T.U.Sukumaran, Professor of Pediatrics, Government Medical College, Kottayam, received the "Best Doctor Award of Government of Kerala for 2002." Congratulation and all the best.

INFECTIOUS DISEASES

MANAGEMENT OF COMPLICATED MALARIA

* *Vidyashankar CV*

Abstract

Complicated malaria occurs mainly in falciparum malaria infections and is predominantly due to hyperparasitemia, which results in microvascular changes. Cerebral malaria, hypoglycemia, anemia, hypovolemia and shock, acidosis, hyperbilirubinemia and intravascular hemolysis are some of the important complications. Appropriate antimalarial treatment with quinine and supportive measures can prevent mortality to a great extent. Newer antimalarials may be necessary in areas with drug resistant malaria.

Key words : *Children, complicated malaria, cerebral malaria.*

With a resurgence in the incidence of malaria, there has been a significant increase in cases of complicated malaria. Complicated malaria mainly refers to complications due to plasmodium falciparum, though complications have been known to occur in infections due to other malarial parasites also. Hyperparasitemia, or infection of more than 5% of the RBCs is thought to be responsible for the various manifestations of complicated malaria. Changes in the infected RBCs, sluggish microvascular circulation and loss of capillary integrity are the likely pathogenic mechanisms.

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Table 1. Complicated malaria – Manifestations

Cerebral malaria
Anemia
DIC
Hypoglycemia
Acute renal failure
Hepatitis
Pulmonary edema
Algid malaria
Blackwater fever due to hemolysis

Clinical features of complicated malaria

Complicated malaria is an emergency. A child presenting with history of fever, altered sensorium, seizures in a malaria prone area has most likely a complicated falciparum malaria infection. Fever in falciparum malaria is persistent rather than the classical tertian description and is usually associated with headache. The manifestations of complicated malaria are listed in Table 1 and are described in detail in this section[1].

Cerebral malaria (CNS manifestations):

Altered sensorium in malaria can be due to cerebral malaria, hypoglycemia or following seizures. Coma in a case of cerebral malaria manifests within 1-2 days of the onset of fever. Post-ictal coma in a case of malaria should be classified as cerebral malaria, only if a child is comatose for over 60 minutes after the seizures. Seizures in cerebral malaria are usually generalized, but partial and subtle seizures manifesting as twitching, dysconjugate gaze, deep breathing, rolling of eyeballs and pursing

Table 2. Cerebral malaria – Clinical features and diagnostic criteria

Clinical features
High fever
Coma
Seizures-generalised, petit mal and subtle
Gaze abnormalities
Retinal hemorrhages
Acidosis and circulatory shock
Diagnosis
Unarousable coma for at least 1 hour after seizures
Presence of asexual forms of parasite in smear
Exclude other forms of encephalopathy

of the lips need to be recognized early. Seizures can also be due to hypoglycemia. Opisthotonic posturing, staring and open eyes and abnormalities in corneal, oculovestibular and oculocephalic reflexes are also present in cerebral malaria, though the pupillary reflex is usually normal[2]. Cerebellar manifestations including nystagmus, ataxia and muscular hypotonia have been described in both the acute phase and as a delayed complication of cerebral malaria[3]. Features of increased intracranial pressure – manifesting as bulging fontanelle, decerebrate posturing and increased CSF pressure have also been described. Retinal examination may reveal hemorrhages. The diagnostic criteria of cerebral malaria are listed in Table 2. While cerebral malaria is a known complication of falciparum malaria, reports of cerebral malaria like picture have been reported in vivax malaria also.

Hypoglycemia commonly presents as altered sensorium or seizures and is hence mistaken for cerebral malaria. It is present in over 5 % of cases of complicated malaria and can occur due to the disease process or as a complication of quinine therapy.

Anemia can be a presenting feature and is due to hemolysis or due to an acute infection complicating a chronic malarial infection.

Bleeding can be a manifestation of complicated malaria and may be due to thrombocytopenia, which is common in falciparum malaria or rarely due to disseminated intravascular coagulation.

Hypovolemia – Circulatory failure and shock can be a presenting feature of complicated malaria. It can occur in association with cerebral malaria or as a manifestation of severe anemia due to hemolysis or in algid malaria. It manifests with cold and clammy skin, tachycardia, tachypnea, hypotension, core-periphery temperature differences, prolonged capillary refill time, decreased skin turgor, dry mucus membranes, fall in blood pressure on standing, oliguria, increased urine specific gravity and low urine sodium.

Respiratory symptoms – Acidotic breathing, manifesting as deep breathing occurs in cerebral malaria and also in children with severe anemia due to hypoxemia. Tachypnea can be a manifestation of shock, pulmonary edema or ARDS. Cough is a common symptom in children with falciparum malaria[4].

Jaundice occurs in complicated falciparum malaria due to intravascular hemolysis and can also be due to malarial hepatitis. Hepatosplenomegaly is present in most children[5].

Oliguria can be due to dehydration, though renal manifestations are per-se uncommon in children. Hemoglobinuria or blackwater fever is another serious and rare complication of malaria and occurs due to severe intravascular hemolysis. It manifests as dark colored urine, hypotension and profound anemia.

Pain abdomen in a case of complicated malaria could be a harbinger of rare and serious complications including spontaneous splenic perforation. Splenic rupture is more common in plasmodium vivax infection and manifests as acute abdomen, guarding, rigidity and shock.

Nonspecific symptoms like vomiting, diarrhea, irritability and refusal of feeds are common in children, more so in endemic areas, where repeated clinical and sub clinical infections result in partial immunity. Adult-pediatric differences also exist in the clinical manifestations of complicated malaria. While seizures, cough, hypoglycemia and acidosis are common in children; jaundice and renal failure are more common in adults with complicated malaria[6].

Investigations

Investigation of a case of complicated malaria involves establishing the diagnosis of malaria and the presence of complications. Despite the advent of various rapid investigation modalities, smear examination remains the corner-stone for the diagnosis of malaria. The various investigations are listed below.

Peripheral smear examination for malarial parasite – Thick and thin smear examination prepared with Giemsa stain and examined under microscope helps in establishing the diagnosis and also the parasite density. Repeated smear examinations are required, as the initial smear examination may be negative. Using a thick smear, a ten fold greater volume of blood is examined, resulting in greater sensitivity. However, as the RBCs are lysed in thick smear, their characteristics cannot be identified.

Fluorescent microscopy (Quantitative Buffy Coat) – Infected RBCs have a lower density than normal RBCs and hence tend to concentrate in the buffy coat. The buffy coat is examined under fluorescent microscope using acridine orange stain, which is taken up by the nucleic acid of the infected RBCs only. This test can be performed within three minutes and is more sensitive than the thick smear examination.

Immunological rapid tests – These tests involve the detection of Histidine Rich Protein 2 antigen (HRP2) and LDH enzyme of the plasmodium. The Paracheck is a strip containing antibodies to HRP2 antigen, which gives a positive result with a drop of blood within 10 minutes. This test has a sensitivity of over 95%. However, the test may continue to remain positive even after treatment, hence it needs to be interpreted with caution in relapses and recrudescences. The Optimals test is another rapid test that detects the presence of LDH in the malarial parasite. This test is different from the Paracheck test in that it can differentiate between plasmodium falciparum and plasmodium vivax infection. These tests can be used in situations where the expertise for microscopy is not available[7].

Other investigations – Hemogram, total leucocyte and differential counts, urinalysis, platelet count, blood sugar, serum bilirubin and transaminases, blood urea nitrogen and serum creatinine, serum electrolytes, arterial blood gas samples for acid-base abnormalities, coagulation profile, chest X-ray and ECG need to be carried out. Leucocytosis, thrombocytopenia, elevated transaminases, hyponatremia, acidosis, elevated BUN and creatinine, hemoglobinuria, proteinuria are some of the common hematological and biochemical abnormalities seen in complicated malaria.

In children presenting with fever and altered sensorium, cerebrospinal fluid examination can help to rule out meningitis and encephalitis. Cerebrospinal fluid pressures and protein may occasionally be elevated in cerebral malaria. Mild pleocytosis (less than 15 cells/microliter) is occasionally present.

Differential diagnosis[3] – Fever is a common presentation in tropical countries. The various clinical presentations of complicated malaria and the important differential diagnosis are listed below.

- Fever, seizures and altered sensorium (cerebral malaria) – Meningitis, encephalitis.

Table 3. Assessment of coma in children – Blantyre Scale[1]

Criteria	Response	Score
Eye movements	Directed	1
	Not directed	0
Verbal response	Appropriate cry or moan	2
	Inappropriate cry	1
	None	0
Best motor response (response to painful stimulus)	Localise pain	2
	Withdraws	1
	Non-specific or absent	0
	Range	0-5
	Unarousable coma	≤2

- Fever with jaundice – Reye's syndrome, leptospirosis, viral hepatitis.
- Fever with anemia – Hematologic malignancy.
- Fever with bleeding – Septicemia, hemorrhagic fevers
- Hemoglobinuria – Drug induced hemolysis.
- Fever with shock – Septicemia.
- Fever with pain abdomen – Enteric fever, amoebic liver abscess, peritonitis.

The most important differentiating features are the presence of fever, splenomegaly and a positive peripheral smear. Other than high opening pressures and presence of mild pleocytosis, CSF is essentially normal and thus helps in differentiation from meningitis and encephalitis.

Treatment

Supportive Care – Vascular access has to be established as soon as possible. If peripheral venous access is not successful, then subclavian or jugular venous cannulation should be done. For emergency administration of fluids to correct shock, intraosseous route can be obtained if other modalities are not successful. Coma is assessed according to the Blantyre's coma scale for children (Table 3). To prevent aspiration, the child is to be nursed in lateral or semi-prone position. Nasogastric tube and indwelling urinary catheter should be placed in critically ill patients. Fever can be controlled with the use of paracetamol through the nasogastric tube or as a suppository and by tepid sponging. Care should be taken to prevent bedsores.

Antimalarials[1] – Early institution of specific antimalarial treatment is the most important factor in reducing the mortality associated with complicated malaria. If clinical suspicion is strong, specific antimalarial should be administered even before the peripheral smear reports are available. The various regimens are listed below. The dose, duration and mode of administration are listed in Table 4. Though chloroquine is the drug of choice in drug sensitive areas, the rapid spread of chloroquine resistance to all parts of the world has necessitated the use of quinine as the first – line drug in complicated malaria.

Treatment is initiated with intravenous quinine followed by oral quinine when the condition is stabilized and continued for a total duration of seven days. If the patient does not respond within 48 hours the dose of quinine should be reduced by 33% (7mg/kg) 8 hourly. Care should be taken to avoid hypoglycemia

Table 4. Antimalarial drugs and dosage

Drug	Route	Loading dose	Maintenance	Duration
Chloroquine	IV infusion	10 mg base/kg over 8 hrs	15 mg/kg over next 24 hrs	
Quinine dihydrochloride	IV infusion	20 mg/kg diluted in 10 ml/kg of isotonic saline given over 4 hours	10 mg/kg 8th hrly (diluted in isotonic saline and given over 4 hours)	7 days
Artesunate	IV bolus	2.4 mg/kg and 1.2 mg/kg after 12 hours	1.2 mg/kg OD for 6 days	6 days
	Suppository	4 mg/kg	2 mg/kg	4,12,48 and 72 hrs
Artetmether	IM	3.2 mg/kg	1.6 mg/kg OD	6 days
Arteether	IM		2.5 mg/kg OD	3 days
Mefloquine	PO	15-25 mg/kg	-	Two divided doses at 12 hours interval
Quinidine		15 mg/kg given over 4 hours diluted in isotonic saline	7.5 mg/kg 8 hrly	7 days
Doxycycline (Age>8 yrs only)	PO		3 mg/kg OD	3-7 days
Clindamycin	PO		10 mg/kg bid	3-7 days

while using quinine. A second oral antimalarial-doxycycline (children aged over 8 years) or clindamycin in those less than 8 years needs to be given for 3-7 days for the rapid clearance of parasitemia and preventing the emergence of drug resistance.

Quinine resistance – In children who do not respond to quinine, artemisinine (quinghaosu) derivatives – artesunate, artemether or arteether need to be given parenterally till the patient is in a condition to tolerate oral administration. The oral formulation, if available, is then continued in the same dosage so as to complete the course. These drugs are to be given in combination with one oral antimalarial–either mefloquine or sulfadoxine/pyrimethamine. Artesunate has the advantage of being administered intravenously and also per-rectally as a suppository in those patients in whom intravenous line cannot be established. It can thus be used for emergency care in a primary care setting.

Management of complications

Cerebral malaria – In addition to antimalarial treatment patients with cerebral malaria need appropriate supportive measures including monitoring the level of consciousness, maintenance of hydration, preventing gastric ulcers with the use of H2 antagonists, hyperthermia and bed sores. Seizures are common in cerebral malaria and can be controlled with per-rectal (0.5mg/kg) or intravenous (0.15 mg/kg) diazepam. Corticosteroids, mannitol and other antiedema drugs have no role in the management of cerebral malaria.

Hyperparasitemia – High levels of parasitemia that do not decline with antimalarials may respond to exchange transfusion.

Table 5. Bad prognostic signs

Clinical	Laboratory
Age less than 3 yrs	Hyperparasitemia (> 5%)
Deep coma	Leucocytosis >12000/cumm
Decerebrate/decorticate rigidity	PCV less than 15%
Pulmonary edema	Blood glucose less than 2.2 mmol/L
Papilloedema	Serum creatinine > 3 mg/dl
Renal failure	Raised venous lactic acid (>5 mmol/L)
Circulatory collapse	Raised CSF lactic acid and low CSF glucose
Absent corneal reflexes	Raised plasma TNF

Hypoglycemia – Hypoglycemia is to be corrected with 0.5g/kg of intravenous dextrose, either as 1 ml/kg of 50% dextrose or 2 ml/kg of 25% dextrose. Intravenous dextrose either as bolus or as a part of maintenance intravenous fluids should routinely be administered to children with complicated malaria.

Fluid and electrolyte abnormalities – Children with complicated malaria are prone to develop dehydration, hyponatremia and acidosis (lactic acidosis). Early identification and treatment including correction of dehydration, electrolyte and acid-base abnormalities and improving the oxygenation are essential. Hypovolemia in circulatory collapse (algid malaria) is to be corrected with plasma expanders or isotonic saline. Correction of acidosis requires the management of dehydration and anemia.

Anemia – Anemia is a common manifestation of severe malaria. Blood transfusion with packed RBC's may be indicated if PCV is less than 12%. These values are not absolute – some children with higher hematocrit may show features of hypoxemia with respiratory distress and impaired sensorium and may need transfusion. Hence the clinical picture needs to be kept in mind when deciding on blood transfusion.

Monitoring[1] - Clinical assessment is very important in a primary care setting, as invasive monitoring may be available only in a few tertiary care centers. The following are some of the parameters that need to assessed.

- Hydration – Avoid dehydration as well as overhydration.
- Hemodynamic parameters – Pulse, blood pressure, jugular venous pressure, capillary refill.
- Temperature – Monitoring of core (rectal) temperature is essential for early identification and treatment of hyperthermia.
- Respiration – depth (acidosis), respiratory rate (tachypnea).
- Look for change in urine colour – hemoglobinuria.
- Sensorium – Coma scale for children.
- Fundoscopy – for hemorrhages, papilledema.
- Blood sugar levels for hypoglycemia.
- Pulse oximetry for SaO_2, arterial pH, central venous pressure and arterial blood gas.
- Response to treatment – repeated assessment of parasitemia.

The various bad prognostic signs are listed in Table 5.

Conclusion

Complicated malaria is associated with a

high mortality. Hence early diagnosis, institution of appropriate treatment and management of complications are important factors that contribute to reducing the mortality.

Points to remember

1. Complicated malaria is predominantly due to plasmodium falciparum infection.
2. Cerebral malaria, hypoglycemia and anemia are the commonest complications.
3. Quinine is the antimalarial drug of choice for complicated malaria

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NEWS AND NOTES

VII RAJNEOCON – 2003 - KOTA

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Venue: IMA House, M.B.S.Hospital Campus, Nayapura, Kota.
Registration Fee:

	Up to 31.8.2003	From 1.9.2003	Spot
IAP / NNF member	Rs.300/-	Rs.400/-	Rs.500/-
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NALS workshop	Rs.400/-	Rs.500/-	-

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INFECTIOUS DISEASES

STRATEGIES FOR CONTROL OF INFECTIOUS DISEASES

** Noel Narayanan S*

Infectious diseases continue to be the leading cause of death among children. Last century witnessed tremendous advances in the discovery of causative organisms for various infectious diseases and the development of control measures for these. Immunization is a success story and its introduction has brought about a dramatic decline in various vaccine preventable diseases. Yet experience teaches us that there is no final victory over infections, for elimination of one problem highlights another and the delicate balance between man and microorganisms remains. Emerging and reemerging infections often resulting from failure of public health programme, pose an important threat to health. Outbreak of communicable diseases and their control still remain a major challenge especially for leptospirosis, cholera, dengue fever and malaria. SARS is the latest addition to this scenario. Years of hard work for eradication of poliomyelitis have not yet met with success and elimination of polio from India appears difficult or impossible. Diarrhoeal disease and acute respiratory infections still remain as major public health problems. Besides, all these infections will lead to a tremendous drain on the scarce resources of developing countries.

Apart from community acquired infections, nosocomial infections pose yet another serious problem for children admitted to hospitals. The increasing prevalence and spread of drug resistant gram-negative bacteria, MRSA and vancomycin resistant enterococci in an ICU set up is an emerging serious problem. The growing population of immuno-compromised children including those with AIDS, represents an increasingly important source of morbidity and death due to infections from innocuous organisms. Constant vigil is essential. Nowadays few undergraduate students have the opportunity to study infectious diseases at the bedside and most enter the profession ill equipped to recognize and deal with common infections. Universal precautions for health care workers often remain only on paper and rarely practiced. Viruses, bacteriae, fungi, parasites and other microbes cause infectious diseases. They can spread from one person to another by several routes.

1. Contact-directly from person to person or indirectly via contaminated equipments, clothes etc.
2. Airborne and droplet infections.
3. Vehicles such as contaminated food, water, blood etc.
4. Vectors such as mosquitoes.

Each pathogen has its characteristic mode of spread and on the basis of this control measures can be undertaken.

Hand washing Sir William Osler once remarked, "Soap, water and common sense are the best disinfectants." Washing hands with soap and water is the most important step in preventing spread of infections through contact. Hands should be washed before and after preparing and

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eating food. Careful hand washing preferably with an antimicrobial soap is important after touching an infected person or contaminated body fluids. This is particularly important in newborn nurseries. Contaminated equipments and surfaces should be cleaned with soap and water and also a disinfectant. Routine cleaning and disinfecting areas like bathrooms and kitchen will reduce the chance for spread of germs.

Universal precaution is an approach to infection control. According to this concept all human blood and certain body fluids are treated as infectious for HIV, HBV and other blood borne pathogens. The new approach 'Standard precaution' is designed to cover all patients in hospitals irrespective of their infection status and has now replaced the previous terminology. This is further reinforced by 'transmission based precautions'.

Airborne and droplet infections

Airborne transmission occurs by dissemination of small particle residue of evaporated droplets that may remain suspended in the air for long time or in dust particles containing the infectious agent eg. measles, varicella, tuberculosis etc. Droplet transmission involves the infected person coughing and sneezing or undergoing airway suctioning etc. Transmission of these large particle droplets requires close contact with the infected person usually within a distance of less than three feet. Eg. H influenzae type b, mycoplasma, meningococci etc. These droplets do not remain suspended in the air and therefore special ventilation precautions are not required in the room, unlike in airborne transmission. Apart from hand washing, use of gloves, gowns and facemasks will also help in preventing transmission of germs. Barrier nursing and isolation preferably in a specially ventilated room with negative airflow is advisable to prevent airborne transmission. Reverse barrier nursing is practiced for immunocompromised children to protect them from environmental pathogens.

Transmission through vehicles such as food, water etc.

Main mode of spread for water borne diseases like diarrhoeal disease, cholera, typhoid etc. is the faeco-oral route. The best way to prevent transmission of these infections is through good personal hygiene, safe drinking water and hygienic consumption of food. Interruption of transmission can be achieved by sanitary disposal of human excreta and disinfection of patient's clothes, stool, vomitus etc. with bleaching powder or 4% hypochlorite solution. Active surveillance is needed for early detection and prompt control before an epidemic occurs. A co-ordinated approach involving the health care workers, water authorities and administrators with public participation is required for rapid relief from an epidemic. The need for strengthening IEC activities on importance of personal and environmental hygiene is equally important.

Vector borne disease

Malaria, Japanese encephalitis (JE) and dengue fever are the major vector born diseases with frequent outbreak in various parts of the country. The three main strategies for prevention of these disease are vector control, animal reservoir control and vaccination if available. Zoonotic disease-leptospirosis is also emerging as a major health problem.

Dengue virus is transmitted by mosquito species belonging to genus Aedes and subgenus stegomyia and JE mainly by Culex mosquitoes. Personal protection from mosquitoes can be achieved to a certain extent by the use of insecticide impregnated mosquito nets and also the popular mosquito mats, coils and liquid

vapourisers. Environmental management to reduce or abolish vector breeding sites and space spraying of adulticides are other methods of control. Community participation again is of utmost importance for the success of any vector control and disease preventive programme.

JE is a zoonotic disease maintained in nature by a complex cycle that involves a variety of vertebrate hosts like pigs, cattle etc. Man is the dead end host. Apart from measures directed at vector surveillance and control, a purified mouse brain derived formalin inactivated vaccine, has been shown to be effective. The dosage schedule is two doses (1ml to adults and 0.5ml for children <3 years) given at intervals of 7-14 days followed by a booster dose 12 months later. Protection is short lived and to vaccinate all succeptible children in JE prone areas is not practicable.

Leptospirosis is another zoonotic infection caused by Leptospira interrrogans which can infect a number of mammals. Rats are the most important reservoir of infection and man is an accidental host. Man acquires infection by direct contact with infected blood, organs and urine of infected animals and more commonly by exposure to any environment contaminated by leptospira (water and soil). Transmission can occur through inflammed or broken skin and intact mucous membranes of conjunctiva, oral cavity and nose. Measures directed at rodent control such as good sanitary disposal of waste and provision of safe water supply are essential. In high-risk groups personal protection is achieved through wearing of protective clothing like impervious boots, gloves and apron. Doxycycline prophylaxis is also effective for exposed adults.

Universal immunization programme and ORT programme for control of acute diarrhoeal disease have been a grand success. However National ARI programme for early detection and treatment of pneumonia has not been so successful.

Prevention of nosocomial infection

An estimated 3-5% children admitted to hospital acquire nosocomial infection. Seasonal viruses, bacteria, fungi and sometimes organisms like MRSA and resistant gram negative bacteria and enterococci are responsible for this. Nosocomial infection causes considerable morbidity and occasional mortality. Intravascular lines, endotracheal tubes, catheters and monitoring devices are all potent sources of infection, especially in intensive care units and newborn special care units. Surveillance for infection is the first step for controlling nosocomial infection. Appropriate infection control measures like hand washing, wearing gloves and gown while handling infected patients are essential. Prudent use of antibiotics should be encouraged. Education of hospital staff regarding spread of infection is crucial to prevent further spread. A multi-disciplinary infection control team consisting of doctors, microbiologists, nurses and administrators can establish practical guidelines for appropriate infection control measures in each hospital.

Specific prophylaxis

Certain infections transmitted by airborne particles or droplets may easily spread to close contacts. Specific precautions are effective to prevent transmission to others.

Following are some examples:

Chemoprophylaxis is recommended to all close contacts

1. Meningococcal meningitis
   Rifampicin 10mg/kg/dose every 12 hourly for 2 days
2. Haemophilus influenza type b meningitis
   Rifampicin 20mg/kg/once daily for 4 days

3. Contact with varicella
   If immunocompromised, varicella zoster immunoglobulin 1 vial (125 units) for each 10kg body wt. IM as soon as possible.
   For normal children-varicella vaccine within 3 days of exposure

4. Pertussis
   To all close contacts if diagnosis is confirmed.
   Erythromycin 40-50mg/kg/day in 4 divided dose for 14 days. Or Azithromycin 10mg/kg/day for 5 days.

Universal precautions for health care workers to prevent transmission of infection in hospitals:

1. Extraordinary care must be taken to avoid accidental wounds from sharp instruments contaminated with potentially infectious material and avoid contact with open skin lesions.
2. Gloves should be worn when handling blood specimens, blood-soiled items, body fluids, excretions and secretions as well as infective surfaces, materials and objects.
3. Gowns should be worn when clothing may be soiled with body fluids, blood secretions or excretions.
4. Hands should be washed after removing gowns and gloves and before leaving the ICU. Hands should also be washed thoroughly without delay, if they had contact with blood.
5. Blood and other specimens should be labeled prominently. All blood specimens should be placed in a second container for transport.
6. Blood spills should be cleaned up promptly with a disinfectant solution, such as sodium hypochlorite.
7. Articles soiled with blood should be placed in an impervious bag before being sent for disposal. Alternatively, such contaminated items may be placed in plastic bags of a particular colour, designated solely for disposal of infectious wastes by the hospital.
8. Needles should not be bent after use, but should be promptly placed in a puncture resistant container used solely for such disposal, needles should not be reinserted into their original sheaths before being discarded into the container, since this is a common cause of needle injury.
9. Disposable syringes and needles are preferred.
10. All procedures involving and manipulations of potentially infectious material should be performed carefully to minimize the creation of droplets and aerosols.
11. Work surfaces should be decontaminated with a disinfectant, such sodium hypochlorite solution following any spill of any potentially infectious material and at the completion of work activities.

(Adopted from PICU manual, JIPMER Pondicherry)

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THE RADIOLOGIST TALKS TO YOU

ALL THAT IS DILATED IS NOT DUE TO OBSTRUCTION.

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In the previous issue we saw that dilatation of the urinary collecting system denotes distal obstruction. But all dilatations do not mean obstruction. Today we will see how this is true.

Look at Fig. 1. The pelvis of the kidney which is not usually seen has distended as a black triangular or oval shadow. This happens when the pelvis is extrarenal without the restraining renal parenchyma around it. The distended extrarenal pelvis should not be mistaken for the dilated pelvicalyceal system of Pelvi ureteral junction (PUJ) obstruction (Fig 2). For this, look carefully for dilatation of the calyces. The calyces are not dilated in the extrarenal pelvis while they are dilated in PUJ obstruction. The distended extrarenal pelvis is not an obstructed system. If in doubt, do an IVU . It will show that the pelvis does empty though after a slight delay.

In Fig 3 look at the dilated pelvicalyceal system. Study the pattern of dilation and compare it with Fig 2 . In Fig 3 the calyces are dilated and the pelvis is also dilated but to an extent smaller than expected. In other words, there is a disproportionate dilation of the calyces when compared to the pelvis. This is a condition called megacalycosis or polymegacalycosis if the number of calyces is also increased. The ureter may or may not be dilated. This is a form of dysplasia of the kidney. Complications like stone formation and recurrent infection can occur. No operation is going to change this abnormality. This condition is best left alone unless the patient is symptomatic.

One notorious problem in children is that of vesicoureteric reflux. When there is no obvious cause for dilation like calculus or posterior urethral valves, consider the possibility of vesicoureteric reflux. Reflux can be unilateral or bilateral. Reflux of grade three and above, when there is dilation of the ureters, can be suspected in a routine ultrasound scan. This can sometimes be confirmed by looking for retrograde flow of microbubbles (agitated saline injected into the bladder) into the ureter. When the bladder contents are turbid due to infection, retrograde flow of turbid contents can also be appreciated. The same principle is extended to colour flow imaging when retrograde flow into the ureters are seen coded in blue or red. To demonstrate retrograde flow continuous scanning of the lower ureter and vesico–ureteric junction is necessary. This is time consuming and not practical. Reflux may not coincide with the time of scanning and high pressure reflux can only be demonstrated when the child voids and sometimes only intermittently. We therefore believe that the best confirmatory test for suspected reflux is the voiding cystourethrogram.

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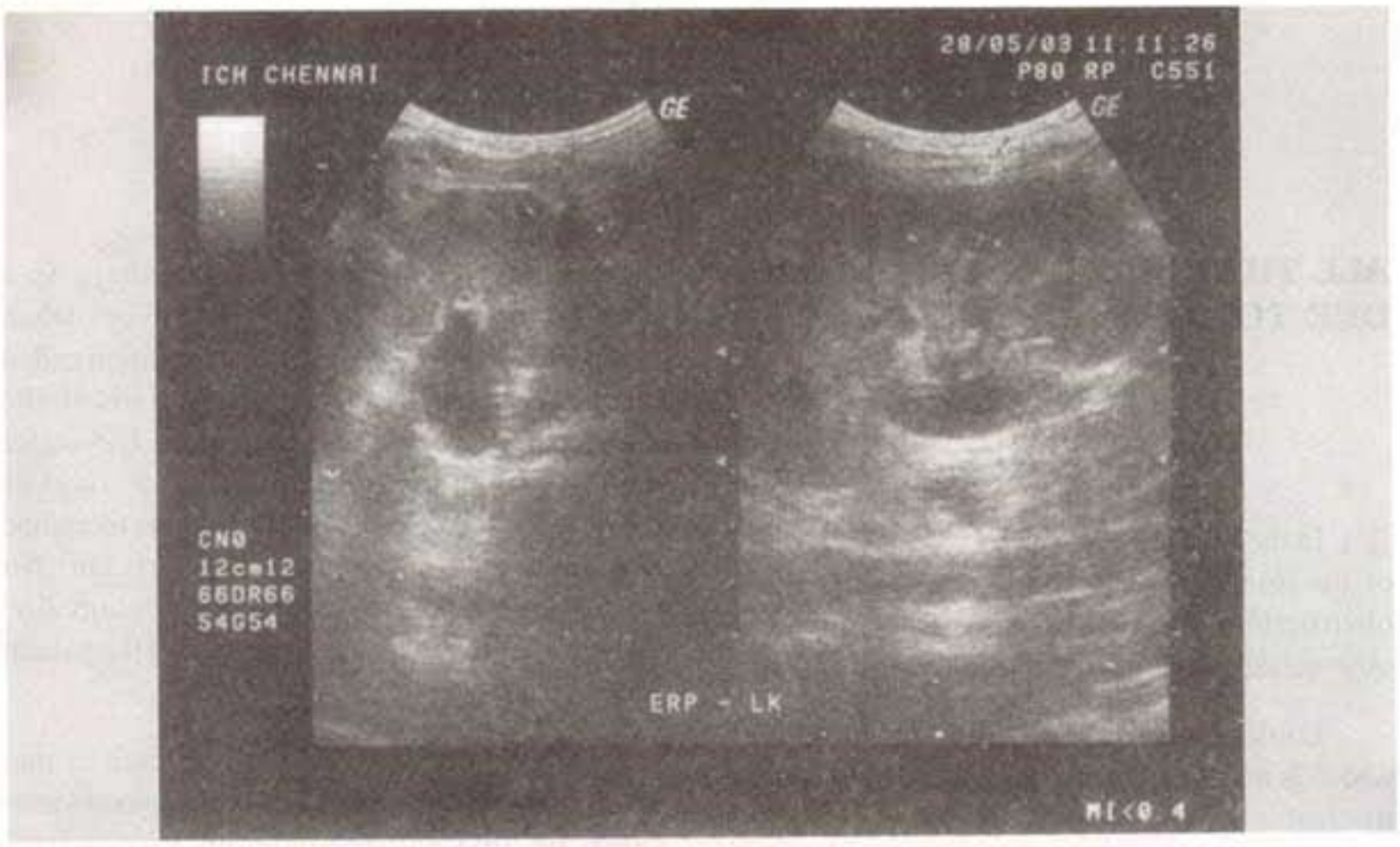

Fig. 1 Extrarenal pelvis

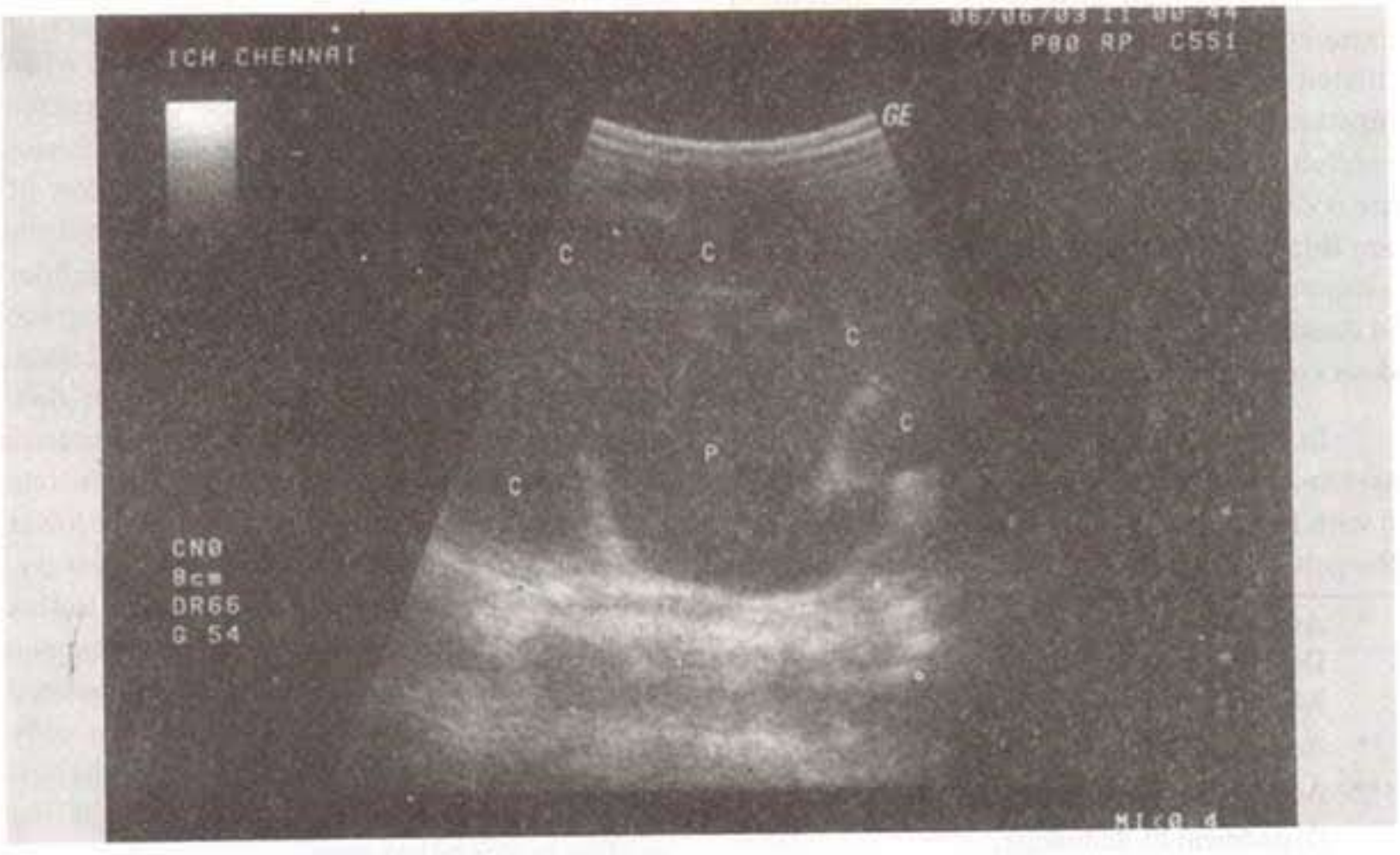

Fig. 2 PUJ obstruction

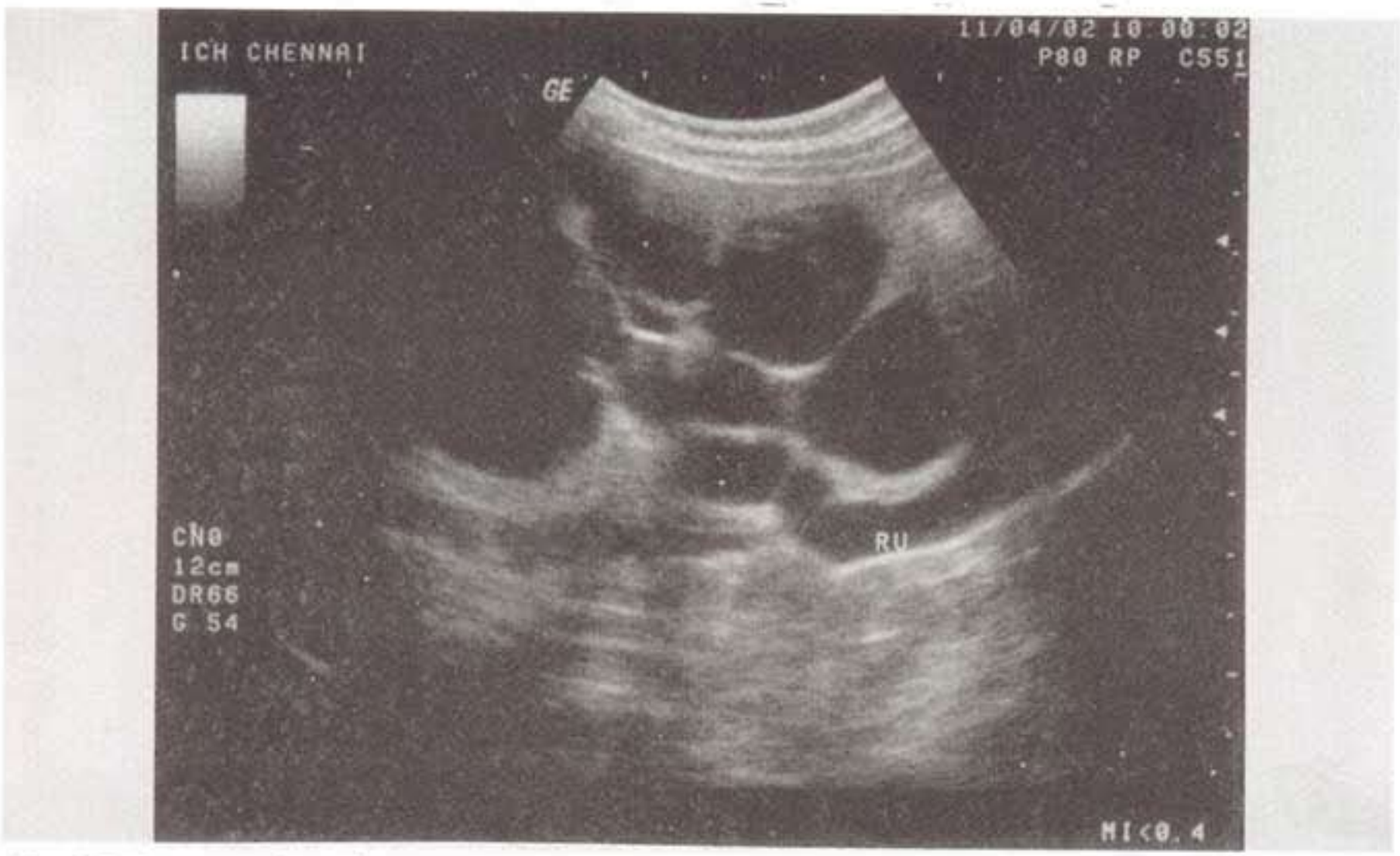

Fig. 3 Polymegacalycosis

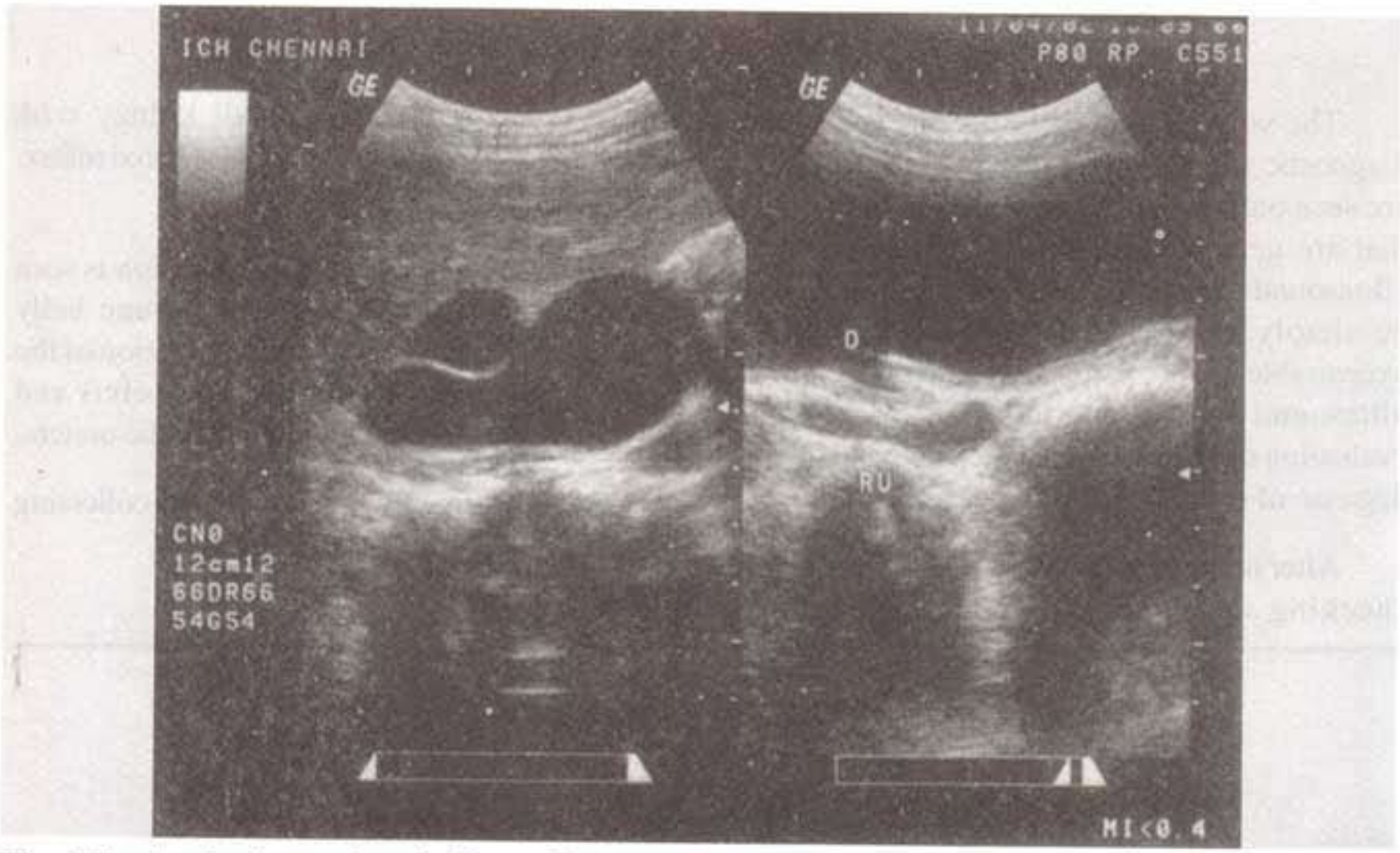

Fig. 4 Ureterohydronephrosis due to Vesicoureteric reflux and reflux atrophy of kidney

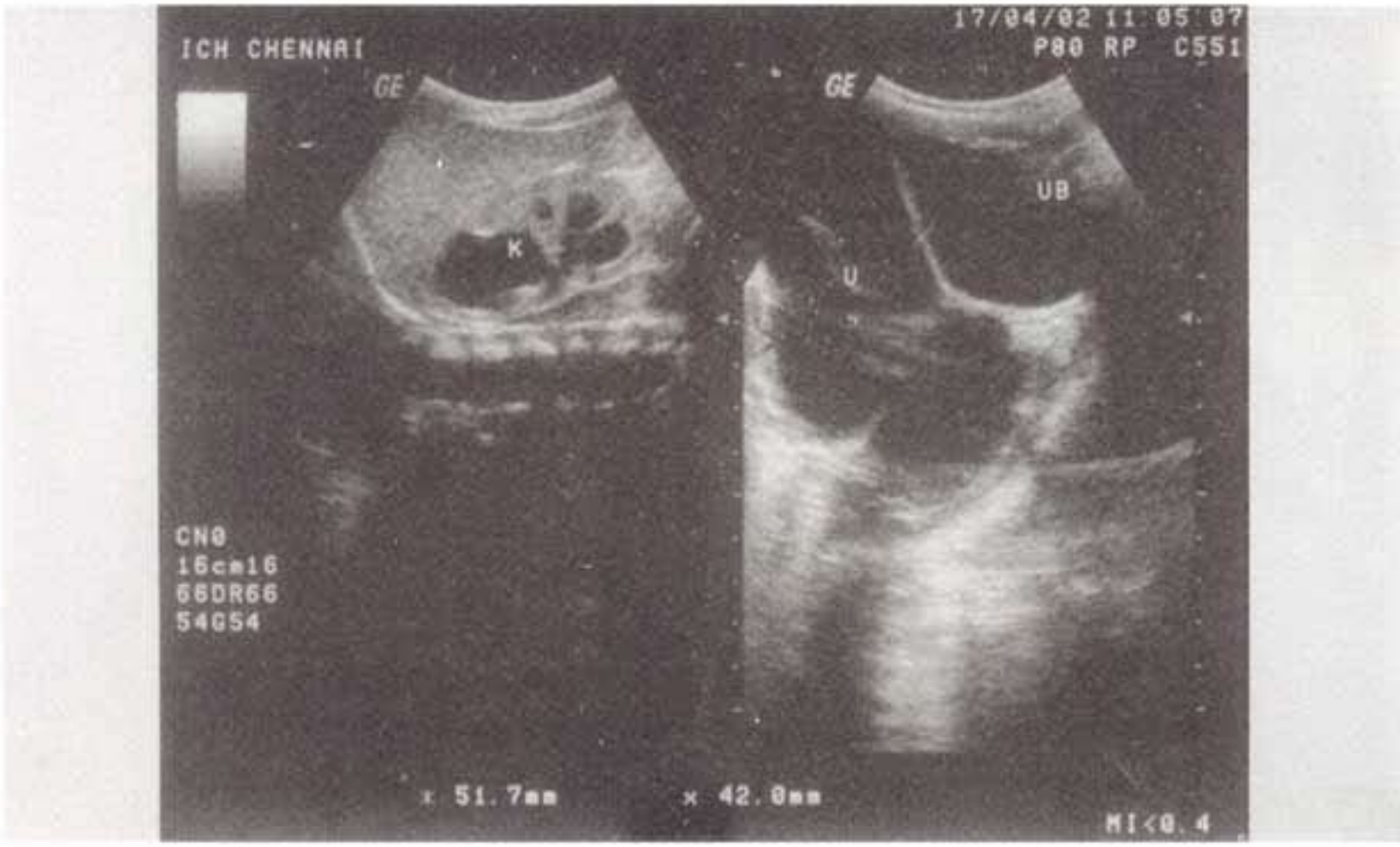

Fig. 5 Prune belly syndrome

The voiding cystourethrogram is also the diagnostic test for lesser degrees of reflux that are seen only with high intravesicular pressures that are generated at the start of micturition. Ultrasound can miss this early reflux which can be simply and effectively treated before irrepairable renal damage results. Therefore ultrasound has to be followed by VCU in evaluation of UTI. VCU can pick up even minor degrees of reflux.

After reimplantation ultrasound is useful for checking the upper collecting system and kidneys. Fig 4 shows a small kidney with ureterohydronephrosis. The VCU showed reflux. So this was a case of reflux atrophy.

One rare condition where dilatation is seen without actual obstruction is the prune belly syndrome. In Fig 5 there is gross dilation of the ureters which are dysplastic. The pelvis and calyces are also dilated but less than the ureters.

So next time you see a dilated collecting system think of these conditions also.

PRACTITIONER'S COLUMN

ANTINUCLEAR ANTIBODY TESTS

** Ketan H.Shah*

Antinuclear antibody (ANA) test is commonly done when connective tissue disorders are suspected in children. The interpretation of the ANA test and the diagnostic possibilities involved are complex. This article tries to simplify this subject.

What is ANA?

Antinuclear antibodies (ANA) are produced against various antigens of the nucleus. A variety of autoantibodies are produced in various rheumatologic and autoimmune diseases. At present, it is uncertain whether the autoantibodies produced in diseases result from an immune response, which is appropriate to an initial antigen, or whether the antibodies are produced because of a defect in lymphocyte regulation. They can be best attributed to abnormal immunological phenomena. Autoantibodies are immunoglobulins, and bind to antigens originating in the same individual or species. The auto-antigen may be protein, nucleic acid, carbohydrate, lipid or a multi-molecular complex.

Types of ANA

Most antinuclear antibodies are of the IgG type; a few are of the IgM type[1]. The reason for continuous production of and persistence of IgM isotype is not known. It is probably a response to a mitogen or cytokines. Specific antibodies are present at very high levels in Systemic Lupus Erythematosus (SLE). Estimates vary from a few hundred micrograms[2] to several milligrams[3] of IgG per ml of serum (equivalent to 0.1-20% of total serum IgG). Some of the antibodies are of IgG1, IgG2, or IgG3 class. Various antigens of nucleus and their functions are shown in Table No.1[4].

Nuclear antigens can be grouped as:

Nucleic acids:

- DNA (Three types: ds DNA, ss DNA and Z-DNA), Histones.

Nuclear proteins:

- Sm antigen, RNP, SSA-Ro, SSB-La.
- Centromere.
- Scl-70 (topoisomerase).

The names can be confusing. Many names are derived from the patients in whom the antigen was first detected. For example, Sm means Smith antigen; it was first detected in a patient named Smith. Scl-70 means Scleroderma –70 antigens. Some antigen names have been derived from the tests or methods used for the detection.

Specific autoantibodies

Antibodies to DNA and DNA binding proteins - Anti-DNA

DNA is carried on chromosomes. Within the nucleus, DNA is compacted and surrounded by proteins. Some of these proteins such as histones are predominantly structural, whereas other proteins regulate transcription (synthesis of RNA) or DNA replication. DNA-histone complexes are

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called chromatin. At least three forms of DNA are antigenic in SLE[3,4] :

- Single stranded DNA : ss-DNA.
- Double stranded DNA : ds-DNA.
- Left-handed DNA : Z-DNA.

Anti ds-DNA antibodies are detected in 60-70% of cases of SLE, and only rarely in other diseases. Detection depends upon the test, method and its interpretation. Therefore variable results may be expected from different laboratories. Presence of Anti-ds-DNA antibodies in SLE has the highest correlation with nephritis. It can be detected by Farr assay[4], ELISA, and Crithidium luciliae trypanosome methods. Indirect immuno-fluorescence (I.I.F.) method will give diffuse/ homogenous pattern under fluorescent microscopy.

Anti ss-DNA antibody has no specific correlation with SLE. It may be present in many other auto- immune disorders, and in various chronic infections.

Anti-histone antibodies:

They are detected in a high percentage of patients with idiopathic and drug induced lupus. Anti-histone antibodies are responsible for the LE cell phenomenon. Many drugs induce various anti-histone antibodies. They are procainamide, quinidine, hydralazine, chlorpromazine. Some other drugs like isoniazid, minocycline and anticonvulsants can also cause drug induced lupus phenomena. In Indian setup we need to remember isoniazid. Antihistone antibodies are also positive in some cases of Juvenile Idiopathic Arthritis.

Anti-ku (ki /nuclear factor iv)

Anti-ku antibodies produce both diffuse, nuclear and nucleolar immuno-fluorescence staining. They are detected in scleroderma / myositis overlap syndrome, scleroderma and SLE.

Anti-PCNA (Cyclin)

The specificity of the antibody is of interest since it only produces positive nuclear immunofluorescence in rapidly dividing cells. This antibody is rarely observed in SLE (approximately 2% cases).

Antibodies to RNA and to ribonucleoproteins - Anti-RNA

Autoantibodies reactive with single and double stranded RNA have been reported in up

Table 1. Various intracellular antigens and their functions.

Antigen	Structure	Function
DNA	Double helix	Template for transcription and replication
Histones	H1, H2A, H2B, H3, H4,	Component of chromatin
Ro (SS-A)	52,60kDa protein	Unknown
	Calreticulin	Calcium binding protein
La (SS-B)	48 kDa phosphoprotein	Transcription termination factor
Sm	B, B', D, and E proteins	Spliceosome components
RNP	68 kDa, A and C proteins	Spliceosome components
U1 RNA	Small nuclear RNA	Spliceosome components
P	P0, P1, P2 ribosomal proteins	Factor binding for protein synthesis
28S RNA	Ribosomal RNA	GTPase domain
Ku/Ki	70 and 80 kDa proteins	? repair DNA termini

to 60 % of patients with SLE[5]. No unique clinical association in SLE is found. They are also found in lower frequency in patients with other autoimmune disorders.

Anti-Sm, Anti-RNP, and Anti-U1 RNA

The Sm (B, B', D, and E) and RNP (A, C, and 68kDa) proteins are complexed with uridine-rich (U) small nuclear RNAs[1,6,7,8] to form small nuclear RNPs (snRNP). Anti-Sm antibody is highly specific for SLE, but its clinical relevance is controversial. Its association with renal or nervous system involvement has been reported and it has been suggested that anti-Sm levels are useful as indicators of disease activity.

The patients who are anti-Sm positive are positive for Anti-RNP also[9]. The converse however is not true. Patients with high titer of anti-RNP and negative anti-Sm frequently have an overlap (Mixed connective tissue disease-MCTD). MCTD consists of some features each of lupus, polymyositis, and scleroderma.

Anti-Ro (SS-A) and Anti La (SS-B)

La is a nuclear phosphoprotein, which binds to RNA Polymerase III transcripts. Ro protein is further characterized to Ro 60 and Ro 52. Calreticulin, a protein involved in calcium binding in the endoplasmic reticulum, has been reported to be a Ro antigen.

The frequency of anti-La and anti-Ro antibody detection depends upon the tests used. Anti-Ro is present in approximately 60% of SLE sera, if immunodiffusion method is used but in less than 20% when western blot technique is used. Conversely, anti- La is detected in approximately 20% of SLE sera by immunodiffusion and 50-60% of sera by blotting. When both tests are employed, anti-Ro and anti-La are almost always both detected in the same sera.

Subsets of anti-Ro also differ in different diseases. Approximately 40% of Sjogren's anti-Ro sera recognize only Ro 52, and 20% of SLE sera bind to Ro 60 but not to Ro 52[10]. Anti-Ro/La antibodies are detected in subacute cutaneous lupus erythematosus(SCLE) and with neonatal lupus erythematosus (NLE). They are also present in Sjogren's syndrome. More importantly they are present in more than 80% of mothers of infants who have congenital heart block when highly sensitive tests such as ELISA or immunobloting are used.

How to detect ANA?

Autoimmune disorders are frequently considered in the differential diagnosis of skin, kidney, joint, lung and other disorders. The simplest screening test is ANA. Nowadays it is routinely performed by Indirect Immuno-fluorescencse test (I.I.F.). It is considered to be gold standard test for detection of ANA.

This test is performed by incubating fixed, permeablized cells (usually Hep-2 cells) on a glass slide with a dilution of the patient's serum followed by addition of conjugated anti-human IgG or IgM. The slide is viewed under microscope and intensity and pattern of fluorescence is evaluated (Table 2).

Important points in this test:

1. Hep-2 (Human epithelioma type 2) cells are used as a substrate. Previously rodent tissues were used. Rodent tissue had very low specificity and sensitivity. Hep-2 cells have largely replaced this Rodent tissue cells.
2. Hep-2 cells allow recognition of over 30 cytoplasmic and nuclear patterns.
3. Human origin cells give better specificity.
4. The nuclei are much larger than any other substrate.

5. Cells are in both interphase and metaphase, so that all cell cycle dependent antigens can be identified.
6. Antigen distribution is uniform unlike with rodent cells.
7. There is no intercellular matrix, so interpretation is easy.
8. Various patterns of immuno-fluorescence are reported, not the name of the antibodies. Various patterns of immuno-fluorescence and their clinical significance is shown in the table No.2
9. Titer is important. More than 1: 80 titer is considered positive. Less than this may be nonspecific which is discussed subsequently.

Primate liver tissue is another substrate. If the test using Hep-2 cells is giving a negative result, the primate liver tissue can be used. Many nuclear antibodies, which are in high titer, are sometimes not detected by Hep-2 cells but detected by primate liver cells. So ideally to label the test as negative, serum from a patient should be negative to both Hep-2 and primate liver cells. However specificity of primate liver cells is low, and it is not practical, so Hep-2 substrate is used routinely

Other methods used for detection of ANA

Gel precipitation, ELISA, Radioimmuno assay (RIA), Western blot, and immunoprecipitation methods are also used. The disadvantage is that they detect specific antigen not the whole group. They can be used as step two test if the ANA is positive with I.I.F. Highly specialized ELISA is available in some part of the world, which may replace I.I.F. in near future. The comparison of various tests is shown in table 3[2].

Indications and limitations of ANA

Some autoantibodies are produced in non-autoimmune, non-rheumatologic conditions also. So a positive ANA does not necessarily mean disease. A negative ANA done with I.I.F. with Hep-2 cell substrate reasonably rules out the possibility of SLE with one exception discussed below. A titer of 1:80 or more strongly supports the diagnosis. Wegener's granulomatosis and polyarteritis nodosa are vasculitis phenomena. In 30% cases of Wegener's granulamatosis and polyarterits nodosa, ANA is positive. Anticytoplasmic autoantibodies are, however more frequently detected in these diseses when neutrophils are used as a cell substrate.

Table 2. Antinuclear antibodies and their patterns of immunofluorescence

ANA pattern	Corresponding antibody	Found in
Rim and/or homogenous (Diffuse)	ds-DNA ss-DNA(LE cell antibody)	SLE, Juvenile idiopathic arthritis, Drug induced lupus
Homogenous(diffuse)	Histones	Drug induced lupus
Speckled Coarse speckled Fine speckled Atypical and other speckled pattern	 Sm,RNP SS-A (Ro),SS-B (la) Scl-70	 SLE, MCTD Sjogren's syndrome Scleroderma
Centromere	???	Crest syndrome
Nucleolar pattern	Nucleolar	Progressive systemic sclerosis

SLE : Systemic lupus erythematosus, MCTD : Mixed connective tissue disorder

Table No.3. Sensitivity and specificity of tests used for detection of various autoantibodies.

Method	Test AG	Sensitivity	Specificity	Application
Immunofluorescence	Whole cell	+++	+	Screening for ANA Detect anti-DNA
	Kinetoplast	+++	++++	Detect anti-membrane antibodies
	Specific cell lines	+++	+	
Gel precipitation	Soluble cell extract	+	+++	Screening Specific antibodies
ELISA	Recombin-ant protein*	++++	+++	Specific detection and quantitation
	Synthetic peptides#	++++	+++	

* The following protein antigens have been cloned and used for detection of antibodies : Ro,La, Smb,RNP,Ribosomal P protein,Ku.

The following synthetic peptide antigens have been used successfully for detection of antibodies: ribosomal P protein, calreticulin, SmB.

Non-autoimmune, non-rheumatologic condition in which ANA is positive

1. Normal healthy individual. He may be a first degree relative of a patient with an autoimmune disease. 40 % of such first degree relatives have a positive ANA without any symptoms. They need to be monitored for development of autoimmune diseases.

2. Drug induced.

   Antiarrhythmic drugs (procainamide, hydralazine).

   Anticonvulsant (phenytoin).

   Other drugs (isoniazid, minocycline).

   In these cases anti-histone autoantibodies are positive. These patients may develop symptoms. Antibodies may persist for months after stopping the drug. They may need treatment if symptoms develop.

3. Hepatic diseases

   Chronic active hepatitis.

   Primary biliary cirrhosis.

   Alcoholic liver disease.

4. Chronic infections.

   Tuberculosis, leprosy.

   Parasitic diseases like malaria, Trypanosoma rhodesiense, Schistosoma japonicum and mansoni, fluke worm (Opisthorchis viverrini).

   Salmonella and klebsiella infection.

   However in these diseases ss-DNA is positive and titer may be low.

5. Malignancies.

   Lymphoma, leukemia, melanoma, and some solid tumors.

6. Hematologic disorders

   ITP, Autoimmune hemolytic anemia.

   Presence of ANA signifies possibility of underlying SLE as an etiology.

7. Hypermobile joint syndrome.

   These patients may have positive ANA. They may not develop symptoms of connective tissue diseases; however they need to be observed for development of autoimmune disorders .

Rheumatologic /Autoimmune causes of positive ANA

1) SLE.
2) Sjogren's syndrome.
3) Polymyositis.
4) Scleroderma.

Table 4. Subset of antibodies and their disease correlation

Antibody specificity	Disease	Incidence
ds-DNA	SLE	60-70%
ss-DNA	SLE	70%
	Drug induced	80 %
Histones	SLE	30-70%
	J.I.A.	15-20%
	Drug induced	95%
Sm	SLE	25-35%
RNP(snRNA)	SLE	30-40%
	MCTD	95%
SS-A/Ro	SLE	30-40%
	Sjogren's syndrome	60-70%
SS-B/La	SLE	15%
	Sjogren's syndrome	40-60%
Scl-70	Scleroderma	70%
centromere	Crest syndrome	80 %

SLE: Systemic Lupus Erythematosus, MCTD: Mixed connective tissue disorder

5) Juvenile Idiopathic arthritis.(In pauciarticular and in polyarticular, not in systemic onset variety)
6) Vasculitis (few cases of Wegener's granulomatosis and polyarteritis nodosa).

Various subsets of antibodies have correlations with particular diseases. They are highlighted in Table 4[11]

The approach to determine cause of positive ANA

In a patient with suspected case of connective tissue disorder ask for specific autoantibodies. In a bonafide case of connective tissue disorder positive ANA will stamp the diagnosis.

Subdiagnosis can be made by the following tips:

I.I.F. ANA negative:

1) If we have a strong suspicion with clinical background for SLE, ask for specific Ro antibody, which may be missed some times, if adequate specifications of tests are not fulfilled.
2) Anti-Jo –1: Not a nuclear antigen, but can be screened to rule out possibility of polymyositis.
3) Anti-Cardiolipin antibody: If we have strong suspicion of SLE with hyper- coagulable state.

I.I.F. ANA positive:

1) Skin and joint involvement (ask for anti-dsDNA, anti-Sm, Anti-Ro). If positive, the most likely diagnosis is SLE.
2) History of exposure to drugs: ask for anti-histone antibodies (If positive, it is drug induced lupus).

3) Dry eyes, dry mouth: ask for anti-La antibody (if positive, it is Sjogren's syndrome).

4) Raynaud's phenomena, sclerodactyly, myositis, telangiectasis, esophageal dysfunction, lung diseases: A positive Scl 70 confirms scleroderma.

A positive centromere pattern in I.I.F. confirms the CREST syndrome.

A positive Anti U1 RNP confirms MCTD.

A positive Anti Jo-1 confirms polymyositis.

Summary

1. ANA detects autoantibodies against nuclear antigens.
2. In a given connective tissue disorder setup, a positive test reasonably stamps the diagnosis.
3. Indirect Immunofluorescence using Hep-2 cells as a substrate is good method for screening.
4. Titer is important, not only positive test.
5. Individual autoantibody detection can be done with other methods.
6. Individual autoantibodies will help in differentiating connective tissue disorders.
7. Many non-collagen vascular diseases, can give rise to false-positive ANA results.

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CASE STUDY

A RARE CASE OF CYANOSIS

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*** Indumathy S*
**** Kulandai Kasthuri*

Case report

A 3 year old male child was brought to the emergency room, Institute of Child Health with acute onset of breathlessness and altered behaviour. The child was apparently normal till he sustained a trivial fall from a tree. There was no history of loss of consciousness or seizures or bleeding. He recovered and 2 hours later, he developed breathlessness, irritability and vomiting. There was no definite history of ingestion of any drug or toxin. Examination in the emergency room revealed central cyanosis, irritability, inappropriate speech and tachypnoea. Cardiovascular and respiratory systems were clinically normal except for central cyanosis, tachypnoea and tachycardia. Pupils were normal. Oxygen saturation by pulse oximetry was 85%. Even with 100% oxygen, his saturation was persistently low and cyanosis persisted. Investigations like CXR, X-ray skull, LFT, RFT, CBC, electrolytes, blood sugar, ECG and CT brain were normal. ABG revealed a normal $PaCO_2$ and PaO_2. So, with this picture of central cyanosis with normal PaO_2 without obvious cardiac or respiratory illness, a possibility of methemoglobinemia was thought of. The blood of the child when examined was chocolate brown in color and did not show any change in color even after exposure to air. Methemoglobin level was estimated to be 46.3%, confirming the diagnosis of methemoglobinemia. After ensuring normal G6PD levels, child was treated with i.v. methylene blue 2mg/kg (in normal saline infused over 5-10 minutes). The child showed gradual improvement and cyanosis and irritability completely disappeared after 4 doses of methylene blue (total of 7mg/kg). Repeat methemoglobin was 3.3% and he was discharged with oral ascorbic acid. The cause for methemoglobinemia was not exactly known. It could have been due to some unidentified toxin ingested by the child.

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Discussion

Methemoglobinemia is the most common cause of cyanosis in the absence of pulmonary or cardiac cause[1]. Methemoglobin is formed by the oxidation of ferrous ion of heme moiety to ferric form. The normal levels are less than 1.5g%. The NADH cytochrome b5 reductase and NADPH dependant methemoglobin reductase are the two important enzymes that maintain the iron in the ferrous form. Methemoglobinemia can be classified into congenital and acquired[2] (Fig. 1).

Congenital methemoglobinemias due to deficiency of cytochrome b5 reductase are of four types, out of which type 2 is the most severe form. HbM is a variant of hemoglobin and is detected by electrophoresis. Drugs like sulfonamides (Dapsone), pyridium, prilocaine, bupivacine,

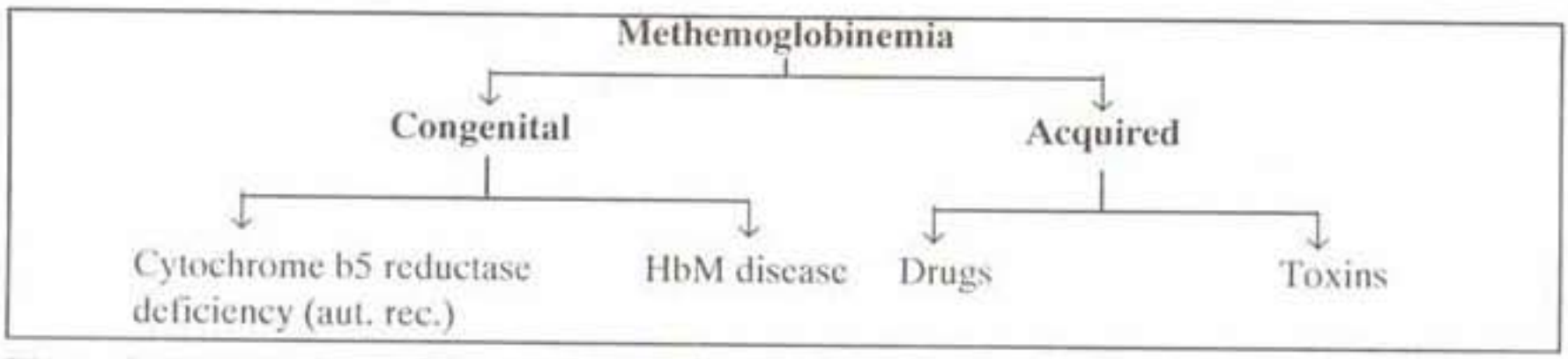

Fig. 1. Classification of methemoglobinemia

primaquine, lignocaine, ifosfamide, metaclopramide, inhaled nitric oxide, vitamin K3 and toxins like aniline dyes, nitrobenzene, silver nitrate, nitrous gases, butyl nitrite, fertilizers well water and food substances rich in nitrates can cause methemoglobinemia[3].

The simple bedside method to identify the condition is to expose the blood of the patient to air. It appears chocolate brown in color and does not turn red on exposure to air (unlike CCHD)[4]. Oxygen saturation by pulse oximetry may be normal[1]. Methemoglobin assays give accurate values. Treatment is indicated if levels are >30% or levels >20% in symptomatic individuals[3]. 2 mg/kg of 1% methylene blue is infused with normal saline over 5 minutes.(Fig. 2) Doses can be repeated and upto maximum of 7 mg/kg can be given[2]. G6PD levels should be determined prior to treatment, as hemolysis can occur in deficient cases[5]. Exchange transfusion is done when levels are greater than 70%, if there is no response to methylene blue and in G6PD deficient individuals. When IV methylene blue is not available, IV vitamin C can be given. In patients with chronic cyanosis, oral methylene blue (100-300 mg/kg/day) or ascorbic acid (300-500 mg/kg) or riboflavin (20-60 mg/day) can be used[6].

The other treatment modalities include hemodialysis, hyperbaric oxygen and drugs like N-acetyle cysteine, cimetidine and ketoconazole. The response to methylene blue is dramatic in toxic methemoglobinemia and child recovers completely without any sequelae[2]. So, in-patients with central cyanosis, in the absence of cardiac or respiratory illness with normal PaO2, methemoglobinemia should be suspected, as early treatment with methylene blue can save these children.

Table 1. The clinical manifestations vary according to the blood levels[2].

Level of methb in blood	Clinical manifestations
<10%	Asymptomatic
10-30%	Cynosis
30-50%	Dyspnoea, headache, irritability, tachycardia
50-70%	Stupor, acidosis, seizures, arrhythmias
>70%	Coma, death

Fig.2 Methemeglobinemia on methylene blue treatment the urine turns blue following infusion of methylene blue.

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NEWS AND NOTES

3RD JHARKHAND STATE PEDICON

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CONGRATULATIONS

Dr.H.Paramesh has been appointed as

1. Chairman, Technical Advisory Committee, Karnataka State Pollution Control Board.
2. Awarded Fellowship of the Indian Academy of Allergy (FIAA).
3. Chief Consultant for World Bank Project on Karnataka State of Environment and Health 2002 – 2003.

CASE STUDY

NEONATAL PROGEROID SYNDROME (WIEDEMANN -RAUTENSTRAUCH)

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The neonatal progeroid (Wiedemann-Rautenstrauch) syndrome is a rare autosomal recessive disorder, comprised of generalized lipoatrophy, hypotrichosis of the scalp hair, eyebrows and eyelashes, relative macrocephaly, triangular face, natal teeth and micrognathia[1]. Only 20 cases have been reported in the world literature till 1999 indicating rare occurrence. Hence we are reporting one such case from Pediatric Department, Medical College, Baroda.

Case report

A fifteen days old male baby was admitted to the pediatric ward of Shree Sayaji Rao Gaekwad Hospital attached to the Medical College, Baroda with complaint of low grade fever since one week. The baby was a product of full term hospital delivery with birth weight of 2200 grams, born without any perinatal complications. There was no history of consanguinity and the elder sib of the patient was normal.

On clinical examination head appeared larger, baby's weight was 2.5 kg, length 48 centimeters and head circumference 35 centimeters with anterior fontanelle 5 x 5 cm and posterior fontanelle 3 x 2 cm and sutures were admitting one finger width. Hypotrichosis of the scalp hair was observed and no hair was found on eyebrows and eyelashes. The head appeared triangular in shape. Dilated veins were visible on the scalp, over chest and abdomen. The skin was thin and showed reticulum like pattern, which was suggestive of cutis marmoratus. There was no natal tooth and the face appeared small with micrognathia (Fig.1).

When the baby was brought to us he was active, alert and sucking well at breast and systemic examination was found to be normal. Complete blood count was normal. Ultrasound of the head did not show any evidence of hydrocephalus. Ultrasound of abdomen was also normal. CT scan of the head did not show any hydrocephalus or congenital malformation like absent corpus callosum. Unfortunately we could not carry out any endocrinal (T3, T4, TSH) and lipid studies nor echocardiography due to financial constraints. Later on the patient was lost for follow up. Considering all morphological characteristics and features, the diagnosis of Neonatal Progeroid (Wiedemann – Rautenstrauch) syndrome was considered.

Discussion

The Neonatal progeroid syndrome (NPS) is a rare disease. Till date probably only about 20 cases are published[1]. The largest series of 5 cases of NPS was reported by Pivnick et al[2].

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NPS is autosomal recessive disorder as evident from literature. There are reports of this disorder occurring in siblings. There are 2 pairs of siblings amongst 5 cases reported by Pivnick[2]. Another study has reported 3 cases, two of which showed siblings with the same disease[3].

NPS is characterized phenotypically by intrauterine or postnatal growth failure, hydrocephalic appearance of head, old man look with prominent veins on scalp and body with sparse hair on scalp, eyelashes, eyebrows and generalized absence of subcutaneous fat with natal teeth. There are long tapering fingers and toes[1,4]. All these features were classically observed in our patient except natal teeth. However it is noteworthy that natal teeth has been reported only in 31.6% cases with NPS. Partial arthrogryposis and cardiac defects like pulmonary stenosis have been reported in a few cases[5] but were clinically absent in our case.

Mental retardation may be seen in some cases[2]. Neuropathology of NPS shows nearly complete absence of mature myelin in the brain. There may be immature myeline sheaths[6]. Skin biopsy shows thin dermis[1] Hutchinson-Gilford syndrome (True Progeria) is differentiated from the NPS as Hutchinson-Gilford syndrome as a rule doesn't manifest congenitally[7].

With increasing age, the appearance of old man remains unchanged[4]. NPS is usually lethal by 7 months and is dependent on severity of neurological impairment. Most cases survive only till late infancy and rarely survive to enter the teens[2,7].

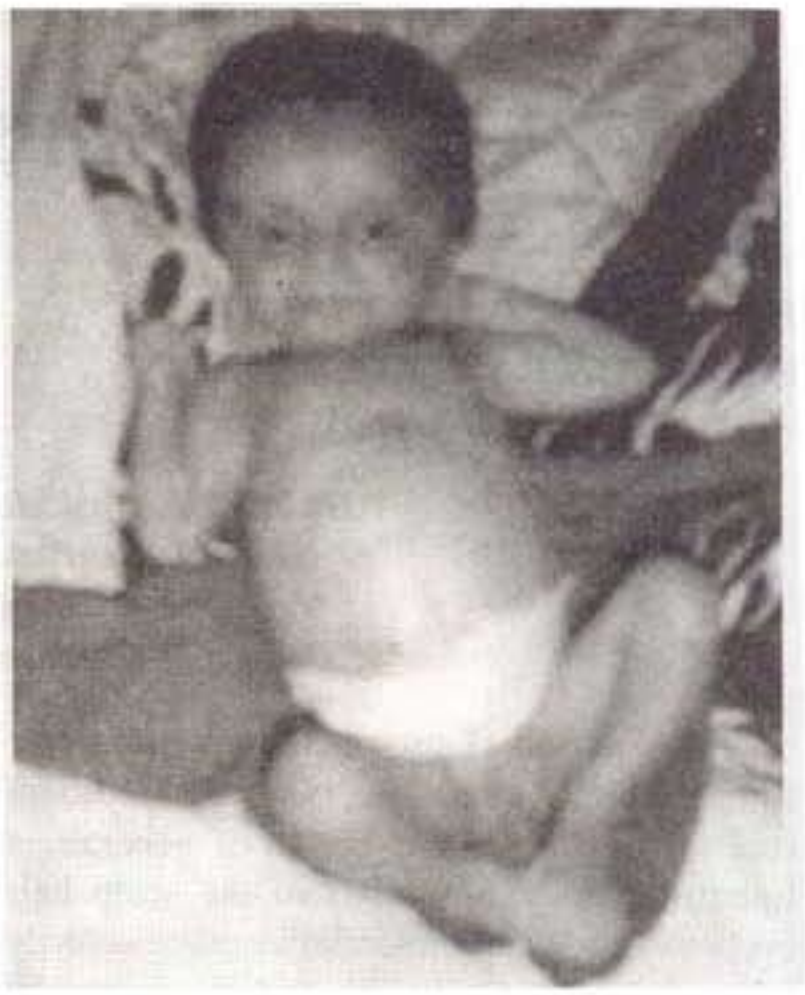

Fig 1. Shows pseudohydrocephalus and absence of eyebrows and eye lashes.

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CASE STUDY

TUBEROUS SCLEROSIS IN NEWBORN – A CASE REPORT

Thiraviam Mohan
Gopal Subramoniam

Tuberous sclerosis is an inherited neurocutaneous syndrome characterized by brain tubers, hamartomas, clinical-neurological signs, seizures and varying degrees of mental retardation, all of which may not be present in the same patient. The presentation in newborn period is most often missed if one is not very meticulous in examining the skin. This case is presented here, because of its rarity.

Case report

A term, male infant was born by caesarian section to consanguinous parents the indication for LSCS being foetal distress. The baby was not asphyxiated at birth and was appropriate for gestational age and the antenatal history was uneventful.

The baby's weight was 2.85kg and length 48cm. On examination there were multiple white macules six in number distributed more over the lower part of the body especially over the legs (fig). Between 50%-90%of infants with tuberous sclerosis have these white macules which become apparent at birth or soon after[1,2]. The head circumference was 35 cms with normal anterior fontanel. The cardiac and respiratory system examination were clinically normal. The fundus examination revealed proliferative changes in retina.

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The complete hemogram and urine analysis were normal. Ultrasonography of cranium and abdomen were normal. The chest x-ray was also normal. CT of brain showed sub-ependymal tubers. ECHO revealed multiple rhabdomyoma arising from the left ventricular walls. Child was active and alert throughout hospital stay and there were no seizures or infantile spasms. Baby was discharged on day 5 of life and advised follow up. The above combination of clinical and radiological findings helped us to make a diagnosis of tuberous sclerosis in this new born.

Discussion

Tuberous sclerosis was first described in 1880 by Bournville[3]. It is inherited as autosomal dominant by sporadic mutation. The incidence ranges from 1:15000 to 1:30000. The classic diagnostic triad of adenoma sebaceum, mental retardation and seizures have been revised to include other manifestations, like skin and systemic signs since many patients with tuberous sclerosis do not exhibit this triad. The gene for tuberous sclerosis has been identified on chromosome 16[4]. The disease affects males and females, equally and 30-40% cases are familial.

The clinical manifestations vary from one patient to another. Ash leaf spots which are hypopigmented, hypomelanotic macules occur anywhere in the body and is often present at birth[5]. Adenoma sebaceum is highly suggestive of tuberous sclerosis and consists of pinkish yellow plaques on malar regions and nasolabial folds, which appear later in childhood or in adolescence. Shagreen patches are areas of shaggy leathery skin typically seen in lumbosacral region. In the brain characteristic

Fig. 1 Hypomelanotic ash leaf macules

Fig. 2 Ashleaf macules in left

lesions include cortical tubers, subependymal nodules and giant cell astrocytomas. When tubers occur, the cerebral architecture is disrupted., which are detected by CT brain or MRI. Patients may present with infantile spasms, seizures, mental retardation or developmental delay. In the heart rhabdomyomas in the ventricular wall occur in infancy, which may result in congestive cardiac failure or cardiac dysarrhythmia. Fundoscopic examination reveals angiolipomas or hamartoma. Renal lesions include renal cysts polycystic kidneys or carcinoma. Other organ systems less commonly affected include lungs, GIT, vascular beds and lymphatics.

The differential diagnosis include other neurocutaneous syndromes with skin lesions, mental retardation and seizures, such as neurofibromatosis, Albright syndrome, incontinentia pigmenti, Von Hippel Lindau disease etc.

Other diagnostic tool is EEG which may show organized pattern of large amplitude, asynchronous sharp waves called hypsarrhythmia. 2D/3D echo cardiography with doppler can detect cardiac rhabdomyomos in various sites and their complications.

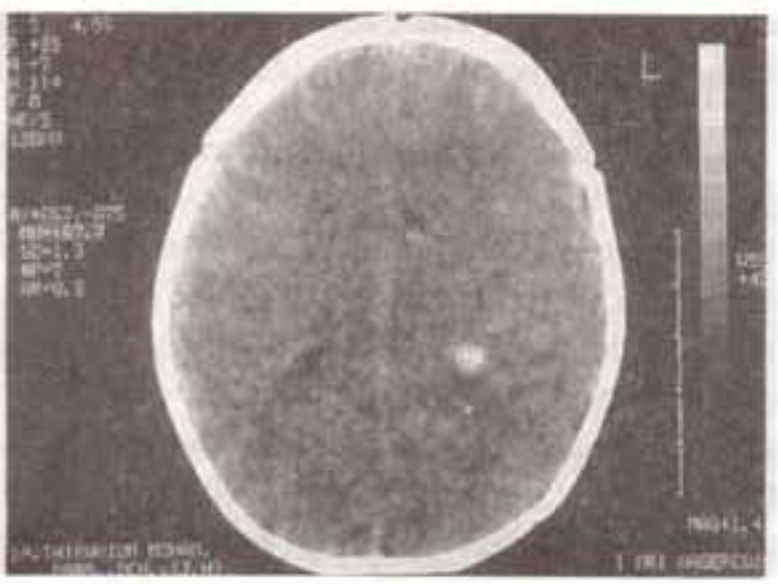

Fig. 3 Calcified subependymal tubers

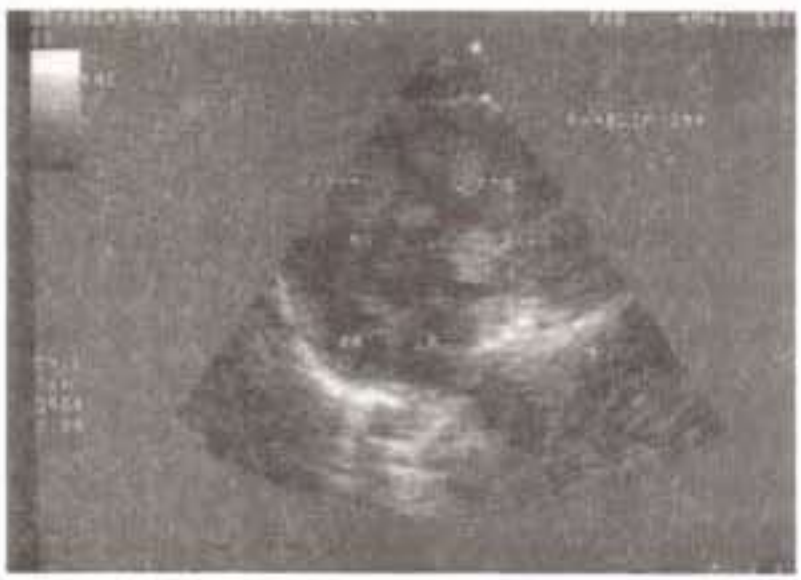

Fig. 4 Rhabdomyoma

Management

Management includes anti convulsant therapy especially ACTH for infantile spasm[1], medical management of congestive cardiac failure or arrythmias in patients who present with cardiac problems. Prognostically seizure control may be difficult. Many children require epilepsy surgery to remove tubers. The affected individual with tuberous sclerosis gene has 50% chance of transmitting the mutation to his or her offspring[2].

Acknowledgement

The authors express their sincere thanks to the hospital authorities, for their encouragement, support and permission to publish this report.

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NEWS AND NOTES

RESPICON 2003 PEDIATRICS

15th National Conference of Pediatric Pulmonology and Respiratory Chapter
Indian Academy of Pediatrics.

Date: 8th - 10th August, 2003.

Venue: Gandhi Medical College, Hyderabad, Andhra Pradesh.

Address for correspondence:

Dr.K.V.Raghava Rao, Chairman Organising Committee,
Dr.N.C.Mathur, Organising Secretary,
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CASE STUDY

GnRH DEPENDENT ISOSEXUAL PRECOCIOUS PUBERTY IN A GIRL CHILD – A CASE REPORT

** Venkataraman P*
*** Sundararaman PG*
**** Karthikeyan AG*

Introduction

Puberty is considered precocious when any of the secondary sexual characteristics appear before eight years in girls and nine years in boys[1]. When the hypothalamo pituitary gonadal axis is activated prematurely it is known as Gonadotropin dependent precocious puberty. More than one sign of sexual maturation with accelerated growth velocity, physical growth and advanced bone age is indicative of gonadotropin dependent precocious puberty[2]. The goals of management are to reverse and prevent further progression of puberty, arrest skeletal maturation and to deal with emotional and psychological problems[3]. Treatment modalities available are GnRH agonists and Medroxy Progesterone Acetate[4]. We are presenting a case of isosexual precocious puberty in a girl child treated with Medroxyprogesterone Acetate.

Case report

Seven year old girl born to non consanguineous parents was brought to the division of Pediatric Endocrinology with complaints of enlargement of both the breasts of six months duration and bleeding per vaginum lasting for five days once a month for two months duration. A developmentally normal child without any history of seizures, headache, blurring of vision, previous CNS infection was found to have a breast size of Tanner stage three, with stage two pubic hair, height percentile of fifty and weight percentile between five and ten. The systemic examinations were normal. With the above findings a working diagnosis of GnRH dependent precocious puberty was made and further laboratory investigation revealed a bone age of nine (chronological age seven) a normal x-ray cone view of sella and normal CT brain. The ultrasonogram of pelvic organs revealed uterine size of 5cm (normal < 3.5cm), ovarian size of 2.6 x 2cm right, 2.5 x 2 left (normal < 1.5cm) which were larger for the age. Hormonal evaluation revealed serum FSH-5.2mIU/ml, LH-13mIU/ml and 17beta Estradiol 20mIU/ml all in pubertal range. Serum 17 OH progesterone and T.S.H. were normal and ultrasound abdomen did not reveal any abnormal findings. With the above clinical, radio imaging and hormonal profile the diagnosis of GnRH dependent isosexual precocious puberty was confirmed. The patient was advised injection Triptorelin, a GnRH analogue 3.75 mg depot preparation i.m. once in 28 days. As the parents could not afford the drug, the next cheaper alternative namely tablet Medroxyprogesterone acetate 10mg b.d. per oral per day was suggested. The patient was reviewed after a period of two months when she showed cessation of menstruation, complete regression of both the breasts to prepubertal stage and a totally absent pubic hair. Height percentile remained the same as before. A repeat ultrasound of pelvic organs revealed a reduction in uterine

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size by 0.1cm. Repeat hormonal assys revealed prepubertal range of FSH (1.6mIU/ml), LH (0.7mIU/ml) and 17 beta estradiol (not detectable). Even though a definitive diagnosis of GnRH dependent precocious puberty can be made by a brisk rise in LH 20 to 40 minutes after infusion of 100mcg of GnRH which is much more than the rise in FSH, the prohibitive cost involving the investigation is a real practical problem. Ultrasonogram of the pelvis that showed a uterine length of more than 3.5cm is a cheaper, highly useful and a reliable cost effective diagnostic parameter in diagnosing GnRH dependent precocious puberty.

Discussion

Ideally, GnRH analogue is the first line of drug, which has a very good effect over the pubertal progression, hormonal parameters and skeletal maturation, but the non-affordability of the parents is a real problem faced by most of the clinicians. The treating clinician is confronted with the problem of parental anxiety, emotional distress, the risk of sexual abuse, early sexual debut and childhood pregnancy at one end and prohibitive cost of GnRH analogue therapy at the other end and is forced to compromise by starting the child with Medroxyprogesterone acetate which is available freely, more economical and is effective in controlling menstruation and secondary sexual characteristics, which definitively renders the needed psychological solatium to the patients and parents alike.

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NEWS AND NOTES

1st NATIONAL MEET ON FLUID, ELECTROLYTES AND BLOOD GASES

Date: 21-23 November 2003.

Venue: Hotel Centre Point, Nagpur.

Contact:

Org. Chairman, Dr.Satish Deopujari

Org. Secretary, Dr.Vishram Buche

Om Child Trust Hospital,
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CASE STUDY

DIARRHEA ASSOCIATED WITH HEMOLYTIC UREMIC SYNDROME: DOES IT ALWAYS CARRY A GOOD PROGNOSIS?

*Nagamani Agarwal
*Kishore D.Phadke
*Arpana Bhagirath
**Isha Garg

Abstract: *We report a case of 'Diarrhea associated HUS' (D+ HUS) in a 4 month old female infant who presented with features of acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia. In view of prolonged oligo-anuria, renal biopsy was carried out which showed extensive cortical necrosis and glomeruli showing fibrin thrombi. There were many poor prognostic indicators like prolonged anuria, younger age and predominantly cortical changes on renal biopsy. The current case highlights the importance of considering various clinical prognostic indicators in predicting the final outcome of D+ HUS patients.*

Key words: *Hemolytic uremic syndrome, prognostic indicators, persistent anuria, younger age, renal cortical necrosis*

Introduction

Hemolytic uremic syndrome (HUS) is characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure (ARF). HUS may be classified clinically as typical or diarrhea associated (D+ HUS) and atypical or sporadic (D- HUS) and histologically as glomerular thrombotic microangiopathy, arteriolar thrombotic microangiopathy or cortical necrosis type[1]. D+ HUS is common under the age of 5 years and is characterised by sudden onset of hemolytic anemia, thrombocytopenia and acute renal injury after a prodromal illness of acute gastroenteritis, usually a bloody diarrhea. Most recover completely. We present here a case of D+ HUS with prolonged anuria who was found to have cortical necrosis on renal biopsy. This case is noteworthy in view of uncommonly significant renal damage following D+ HUS despite prompt and adequate management.

Case report

A four month old female infant presented with loose stools and high grade fever of 8 days duration with lethargy, poor feeding and decreased urine output of 2 days duration. There was no blood or mucus in stool. Pre-admission medication details were not available. Child was sick, irritable, febrile with pallor and moderate dehydration. Her blood pressure and systemic examination was normal. A provisional diagnosis of sepsis, with acute gastroenteritis and dehydration was made. Anuria persisted after correction of dehydration.

Investigations are as follows. Urine examination revealed 2+ proteinuria with plenty of RBC's and red cell casts. Total WBC was 26,000 cmm with predominant neutrophils. Platelet count was 20,000 lacs/cmm, Hb 6.7 gm/dl and peripheral smear showed Burr cells, Helmet cells, Fragmented RBC suggestive

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of microangiopathy. Reticulocyte count was 1.5%. Prothrombin time and activated partial thromboplastin time were normal. B. urea was 103 mg/dl, S. creatinine 2.8 mg/dl with normal S. electrolytes. Blood and stool culture was negative. Stool microscopy showed 2-4 pus cells and was negative for occult blood. CSF analysis was normal. Renal scan showed bilateral grade II parenchymal disease. Based on the above clinical and laboratory findings, the diagnosis of D⁺ HUS was made.

She was managed by peritoneal dialysis and other supportive measures. As she remained anuric for 13 days a renal biopsy was done which showed extensive cortical necrosis with occasional glomeruli showing fibrin thrombi and fibrinoid material in the blood vessels. Her urine output improved and was discharged with a platelet count of 2.5 lacs/cmm, Hb 11.2 gm/dl and S.creatinine 2.6 mg/dl. One month after discharge the S. creatinine was 2.5 mg/dl and was on conservative treatment for chronic renal failure.

Discussion

D⁺ HUS has been associated with good prognosis and high recovery of renal function. Fitzpatric et al[2], in a follow up of D⁺ HUS cases reported a lower acute mortality (3%) and fewer children progressing to end stage renal failure (3%) whereas Srivastava et al[3], reported an acute mortality 60% with severe renal damage. It is the D⁻ HUS that has been associated with recurrence and even persistence of microangiopathic process and consequent clinical manifestation of HUS and progression to hypertension and chronic renal failure. In this child with D⁺ HUS, there was an extensive renal pathological change such as cortical necrosis, fibrin thrombi in the glomeruli and fibrinoid material in the blood vessels. All these are indicative of poor renal recovery. Clinically features of poor outcome as expressed in this child are persistent anuria and very young age.

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NEWS AND NOTES

PALS PROVIDER COURSE

The course will be conducted at the Department of Pediatrics, Govt. Raja Mirasdhar Hospital, Thanjavur attached to Thanjavur Medical College.

Date: 14.9.2003 and 15.9.2003.

Registration is restricted to 40 delegates on first come first served basis. No spot registration.

The registration fee is Rs.1000/- (including course material) to be sent as demand draft only drawn in favour of Dr.N.Ganga, Thanjavur.

Contact Address:

Dr.N.Ganga, Professor of Pediatrics, Govt. Raja Mirasdhar Hospital, Thanjavur, Tamilnadu.

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IJPP-IAP CME MATERIAL

APPROACH TO A CHILD WITH PERSISTENT JAUNDICE

** Kumutha J*

A jaundiced infant is a common problem that confronts a pediatrician daily. The new born infant is unique in this regard not only because of limitations in the metabolism and clearance of bilirubin but also because this is the period of life when elevation of serum bilirubin may be toxic to the infant's developing brain.

Hyperbilirubinemia is a benign condition in most infants.But some babies may show persistent elevation in the levels of bilirubin in the neonatal period, thus causing concern.

Persistent jaundice: Visibly detectable jaundice beyond two weeks of age in term infants and three weeks in the preterm infants merits the description of persistent or prolonged jaundice. The causes for this may be unconjugated or conjugated hyperbilirubinemia.

The common causes for persistent unconjugated hyperbilirubinemia are:

- Persistence of acute neonatal illness like hemolytic disease of newborn due to feto-maternal blood group incompatibilities.
- Breast milk jaundice
- Hypothyroidism.
- Concealed hemorrhage (Cephalhematoma, subgaleal bleed, intra cranial bleed etc)
- Pyloric stenosis and conditions with organic or functional intestinal obstruction.
- Trisomy 21
- Crigler – Najjar syndrome

The common causes of persistent conjugated hyperbilirubinemia are:

- Idiopathic neonatal hepatitis.
- Infections eg. TORCH;Hepatitis A,B,C; Coxsackie virus and others.
- Bacterial sepsis.
- Extrahepatic biliary atresia.
- Choledochal cyst.
- Inspissated bile syndrome.
- Total parenteral nutrition.
- Intrahepatic biliary atresia.
- Metabolic disorders (galactosemia,alpha-1 antitrypsin deficiency,cystic fibrosis)
- Chromosomal anomalies.

Clinical assessment of bilirubin level:

In newborn, jaundice is detected by blanching the skin with digital pressure, thus revealing the underlying colour of the skin and subcutaneous tissue. This dermal icterus is seen first in the face and then progresses in a caudad manner to the trunk and extremities..Kramer studied[2] the relation between the progression of dermal icterus and serum bilirubin levels(Fig.1)

Jaundice of the Face	: 5 mg%
Face and trunk	: 10 to 15 mg%
Face, trunk, soles & palms	: > 15 mg%

Approach to diagnosis includes

History (Table 1), Physical examination (Table 2), Investigation (Table 3).

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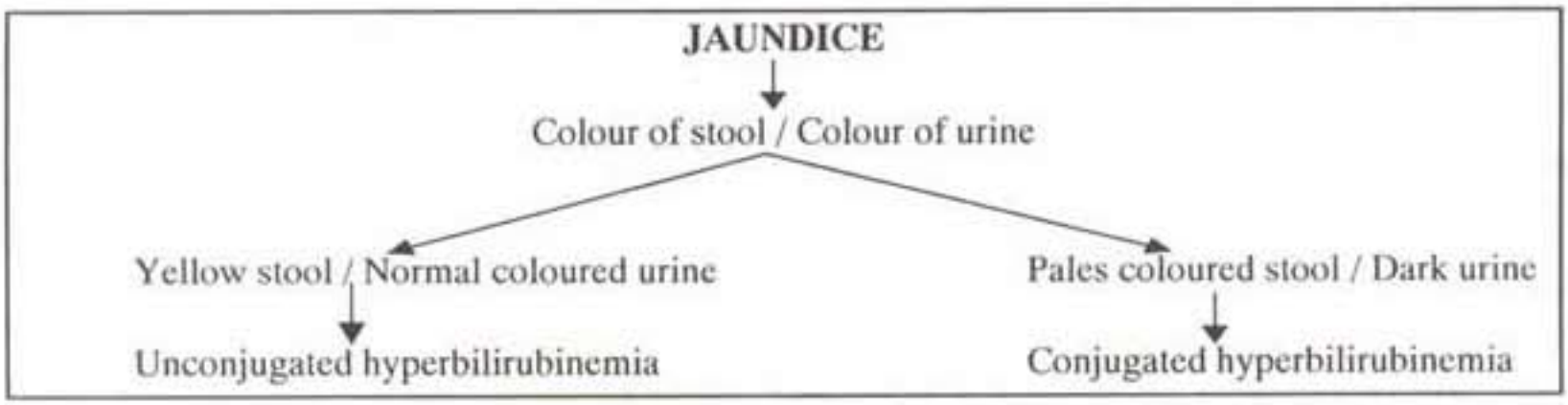

Fig. 1. Approach to a newborn jaundice

Table 1. Persistent unconjugated hyperbilirubinemia

History	Suggestive diagnosis
• Previous sibling with neonatal jaundice	: Rh, ABO, incompatibility,Hereditary Spherocytosis
• Familial Jaundice	: Crigler Najjar, Gilbert
• Instrumental delivery	: Concealed hemorrhage
• Breast feeding	: Breast milk jaundice
• Delayed passage of meconium & infrequent stools	: Hypothyroidism / Hirschsprung's disease.
• Vomiting	: Pyloric stenosis
• Drug ingestion	: G-6-PD Deficiency
• Increased maternal age	: Trisomy 21

Table 2. Physical examination

• Cephalhematoma / Subgaleal bleed	: Extavasated blood
• Plethora	: Polycythemia
• Pallor & Hepatosplenomegaly	: Haemolytic anaemias
• Pallor / Anemia/ Shock	: IVH
• Umbilical hernia	: Hypothyroidism
• Facial dysmorphism	: Trisomy 21

Table 3. Investigations

• Serum bilirubin (Total /Indirect)	• Blood group and type (Mother & Infant)
• Coomb's test on neonate's blood	• Reticulocyte count
• Peripheral blood smear	• Thyroid function tests
• Abdominal ultrasound	• Karyotyping
• G6PD levels	

Unconjugated hyperbilirubinemia may be due to these processes

- Excessive hemolysis
- Decreased / absent transferase activity.
- Increased entero-hepatic circulation.

Haemolytic disease of newborn: Feto-maternal blood group incompatibility produces persistence of jaundice due to excessive continued hemolysis.

Hypothyroidism: Jaundice is due to delayed maturation of the ability of the liver to conjugate bilirubin because of hormone dependent variations in uridine diphosphate glucuronyl transferase activity.

Breast milk jaundice

A strong association has been found between breast feeding and an increased incidence of neonatal hyperbilirubinemia. The jaundice may appear early (2-4 days) & later (4-7 days of age). The early onset jaundice has been called *breast feeding jaundice* and the late onset jaundice is called *breast milk jaundice*. It has been suggested that inadequate lactation during the first few days and the relative starvation accompanied by increased weight loss may account for the early elevation of bilirubin. Several studies have suggested that substances present in the breast milk,such as pregnanediol, lipase or fatty acids inhibit bilirubin conjugation by glucuronyl transferase. The jaundice also results from increased intestinal reabsorption of bilirubin by an exaggerated entero- hepatic circulation.Breast feeding should not be interrupted, because seldom in infants levels more than 20 mg % are reached even with continued breast feeding. There has been no documented evidence of bilirubin encephalopathy in breast milk jaundice. Reassurance is all that is needed and if needed phototherapy can be given.

Extra vascular blood

Sequestrated blood as in cephalhematomas or sub-galeal bleeds leads to hyperbilirubinaemia because of excess bilirubin production resulting from break down of hemorrhagic red blood cells.

Management

1. • Phototherapy
   • Surgery – Obstructive lesions
   • Hormone replacement – Hypothyroidism
2. Phenobarbitone- Enzyme induction
3. Specific therapy

Conjugated hyperbilirubinemia

Conjugated hyperbilirubinemia can arise from any pathology which prevents excretion of conjugated bilirubin from the hepatocyte into the duodenum. Clinically the diagnosis is suggested by hepatosplenomegaly, pale stools and dark urine. This phenomenon is better described as cholestasis since there is not only retention of conjugated bilirubin but also bile acids and other compounds leading to fat malabsorption and steatorrhoea (Table 4 and 5).

There is growing consensus that the two common causes of conjugated hyperbilirubinaemia. idiopathic neonatal hepatitis and extrahepatic biliary atresia may be the opposite ends of a single spectrum of disease and that pathologic process observed is dynamic. The

Table 4. History of conjugated hyperbilirubinemia

History	Suggestive diagnosis
• H/O Liver disorder /Jaundice in previous sibling	: Inherited disorder,Dubin Johnson and Rotor syndrome
• Unexplained febrile illness during pregnancy	: Congenital infections
• Prematurity /SGA	: Congenital infections, neonatal hepatitis
• Lethargy, poor feeding, vomiting	: Bacterial sepsis, Congenital infections
• Poor feeding and seizures	: Metabolic disorder
• Bleeding tendency	: Hepatocellular failure
• Prolonged parenteral nutrition	: Cholestasis

Table 5. Physical examination - Conjugated hyperbilirubinemia

Prematurity / SGA	:	Neonatal hepatitis
Microcephaly	:	IU infections
Petechiae	:	IU infections
Pallor	:	Sepsis / Inspissated bile
Omphalitis	:	Sepsis
Hepatosplenomegaly	:	IU infection,sepsis, extrahepatic biliary atresia neonatal hepatitis, metabolic
Fundus – Chorio-retinitis	:	IU infection
Cataract	:	IU infection & Galactosemia
Cystic mass below the liver	:	Choledochal cyst
Situs inversus with/without polysplenia	:	EHBA

probable undefined insult causes inflammation of liver cells or cells of the biliary tract. If the site of disease is predominantly biliary duct epithelium there is cholangitis followed by sclerosis, narrowing of the biliary tree and complete obliteration causing extrahepatic biliary atresia. On the other hand injury to liver cells may present with features of neonatal hepatitis (Table 6).

Idiopathic neonatal hepatitis (NH)

Idiopathic neonatal hepatitis occurs either as sporadic or a familial form. Prolonged conjugated hyperbilirubinaemia is of unknown cause. There is no evidence of generalized viral illness or an identifiable infectious agent. The familial incidence is 10 to 15%. The prognosis is poor with familial form (recovery less than 30%) Neonatal hepatitis is common in low birth weight and preterm infants. Jaundice develops during the first week. A wide variety of clinical presentations may occur from severe failure to thrive or fulminant hepatic failure to asymptomatic jaundice. The colour of the stools is variable. Physical examination reveals firm hepatomegaly. Liver biopsy may be helpful in making the diagnosis. Management is towards nutritional support and medical management of complications . The prognosis is variable with 50% of cases resolving with little or no sequelae. But some may progress to life threatening liver disease.

Extra hepatic biliary atresia (EHBA)

EHBA is the most frequent surgically correctable liver disorder in infancy affecting 1:14000 of live births. It is characterised by luminal obliteration or absence of all or segments of the extra hepatic biliary system. Recent evidences suggest that biliary atresia may result from a developmental aberration causing failure of intrauterine remodelling process at the hepatic hilum with persistence of poorly supported foetal bile ducts. No known familial pattern has been demonstrated. EHBA may be associated with polysplenia heterotaxia syndrome , vascular abnormalities below the diaphragm ,asplenia and chromosomal abnormalities in 10 to 15 % of cases.

The specific problems in the diagnosis of biliary atresia are the following:

- The extrahepatic and intrhepatic bile ducts may be patent in the first few weeks of life before complete obstruction of bile flow occurs. Thus stools might be yellow in the first few weeks.
- Infants are often well nourished ,apparently well looking in the first few weeks of life

Table 6. Features Differentiating Neonatal Hepatitis and EHBA

Features	NH	EHBA
Familial Incidence	20 %	Nil , but assoc.anomalies
Birth Weight/Gest. Age	LBW / Preterm	Term / AGA
Presentation of Jaundice	Anytime during neonatal period	2-4 weeks
Dark Urine	Present	Present
Hepatomegaly	Moderate /Firm	Larger / Often hard
Splenomegaly	Early	Late
Acholic Stool	Transient /Incomplete	Present
SGOT / SGPT	Severe derangement	Mild to moderate
SAP	+	++
Serum AFP	May be increased	Absent
Hepatobiliary Scintigraphy	Sluggish uptake; excretion into intestine eventually occurs	Normal uptake; excretion into intestine absent.
Liver biopsy	Diffuse hepato –cellular disease ; distortion of lobular architecture (Giant cell predominance)	Ductular proliferation ; hepato- lobular architecture intact.
Operative Cholangiography	Normal	Block may be visualised
UGI – Endoscopy	Bile seen in duodenum	Bile not seen

causing little doubt in the minds of paediatrician and health workers.

- Jaundice gradually develops between 3 to 6 weeks. Many times appears to be a continuation of physiologic jaundice.
- Variable intensity of jaundice alternately deepening and lightening.
- Sometimes stools may be coated with sloughed heavily jaundiced epithelial cells. This covers the core of the stool which is clay coloured.

It is essential to refer infants with acholic stools early because the longer the biliary atresia has been present , the greater is the likelihood that the intrahepatic bile ducts will have been obliterated and porto- enterostomy will be less likely to be successful. Hence early surgical intervention is essential to avoid progression of biliary cirrhosis. This progression leads to death by the age of 2-3 years. The bile flow is significantly greater after porto –enterostomy in infants operated on ,before 60 days of age (91%), compared with those operated after 3 months of age (17%).

Inspissated bile syndrome

A proportion of infants seriously affected by severe red cell haemolytic disease may have prolonged jaundice with high proportion of direct reacting bilirubin. This is also seen in infants with hydrops foetalis or infants treated with intrauterine blood transfuion or exchange transfusion.Transient disparity between the maturity of the conjugating and excretory functions of hepatocytes is present and jaundice is due to sludging of bile pigments within bile ducts. The prognosis is generally good and jaundice eventually disappears without any specific therapy and can be diagnosed by ultrasonography. But other causes should be excluded.

Total parenteral nutrition

Prolonged intravenous nutrition causes cholestasis and hepatocellular damage which may

progress to cirrhosis. The pathologic process is not clearly defined, although aminoacids, ,lipids and trace element toxicity have been implicated. Prevalence increases with degree of immaturity,duration of intravenous fluids and absence of oral intake. TPN produces acute acalculous cholecystitis, biliary sludging and causes cholestasis. There is conjugated hyperbilirubinaemia ,hepatomegaly and abnormal liver function test. Most abnormalities resolve once TPN is ceased.

Investigations for conjugated hyperbilirubinemia

- Bilirubin levels (Total / direct)
- LFT (SGOT,SGPT,SAP)
- PT and PTT
- CBC and Reticulocyte count
- Serum glucose and electrolytes
- Urine routine examination and screening for metabolic disease
- Blood group and typing of infant & mother
- Torch panel & HBs Ag screening
- Septic screen (blood ,CSF and urine culture)
- Abdominal ultrasonography
- Hepato biliary imaging
- Upper GI -endoscopy

Special tests

- Percutaneous liver biopsy
- Exploratory laparotomy
- Operative cholangiogram
- Metabolic screening for specific disorders
- Sweat chloride test and immuno reactive trypsin

The first priority is to identify the causes and complications for which urgent treatment is required.Exclude septicemia, urinary tract infection, intrauterine infections like syphilis, CMV, ,metabolic disorders like galactosemia and fructosemia and EHBA. After the initial necessary investigations, an ultrasonogram should be done. This will reveal mechanical problems such as choledochal cyst, inspissated bile syndrome and spontaneous perforation of bile duct. If infective, metabolic or viral causes are confirmed with patent biliary system as evidenced by USG no further investigation may be needed. In most cases however hepatobiliary scan with Tc99M imino diacetic acid (HIDA) and liver biopsy may be needed to rule out EHBA and idiopathic neonatal hepatitis. Phenobarbitone 5 mg/kg/day given per 5 days prior to the scan, helps the biliary excretion and is useful in distinguishing infants who do not have biliary atresia

In EHBA there is normal uptake with absent excretion. Upper GI endoscopic visualisation of bile in duodenum also helps in excluding EHBA. Confirmation of the diagnosis and treatment requires cholangiogram and wedge biopsy of the liver.

Management of conjugated hyperbilirubinemia

Promotion of bile flow: Phenobarbitone and Cholestyramine promote bile flow and decrease level of bilirubin and bile salts. Cholestyramine is a non absorbable anion exchange resin that irreversibly binds bile salts in the intestine , which leads to increased fecal excretion of bile salts.Ursodeoxy-cholic acid (UDCA) has also been successfully used along with phenobarbitone and cholestyramine. The dose of UDCA is 15 mg/kg/24 hrs.

Prevention of malnutrition and vitamin deficiency: Long chain triglycerides are poorly absorbed in the absence of sufficient bile salts. Hence diet should include medium chain triglycerides(MCT) which can be absorbed without action of bile salts. Breast fed infants can be fortified with MCT (coconut oil).

Fat malabsorption will also interfere with maintenance of adequate levels of fat-soluble

vitamins in these infants. Supplementation with vitamin A D E & K is suggested.

Dose

Vitamin A: 10,000 to 15,000 IU/day (Aquasol-A)

Vitamin D: 5,000 to 8,000 IU/day of vitamin D2 or 0.5 g/kg/day of 25-hydroxycholecalciferol.

Vitamin E: 50 to 400 IU/day as oral alphatocopherol

Vitamin K: 2.5 to 5mg every other day, may be necessary to prevent bleeding tendency.

Dietary restriction:

Removal of galactose, lactose, fructose, sucrose may prevent development of cirrhosis.

Surgical management

Laparotomy with biopsy should be done if EHBA is strongly suspected. Other causes for which surgical management is possible are choledochal cyst, spontaneous rupture of bile duct, lymphnode enlargement and tumors. Cystic fibrosis induced inspissation may also require the surgical removal of tenacious plugs.

Kasai procedure: Hepatic portoenterostomy is the surgical procedure needed for EHBA. Optimal results are obtained if done at <8 weeks of age. Even if the procedure is successful however most infants will progress to cirrhosis as the result of ongoing hepatic inflammatory sclerosing process.

Liver transplantation

Orthotopic liver transplantation is the definitive therapy of bilary atresia. When end stage liver disease is inevitable, liver transplantation may be done. Currently 50 to 70% of infants are alive,one year after surgery.

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NEWS AND NOTES

NATIONAL WORKSHOP ON PEDIATRIC EMERGENCY PROCEDURES

Organized by: Department of Pediatrics, Sir Ganga Ram Hospital and IA Pediatric Intensive Care – Emergency Cell.

Date and Venue: 15 th – 16th November 2003 at Sir Ganga Ram Hospital, New Delhi.

Registration Fee: Rs.1500/- by Cash/Cheque/Demand Draft in favour "Ambulatory Pediatrics" at Delhi. (Registration limited to 50 delegates)

Correspondence:
Organizing Chairman, Dr.P.K.Pruthi (981104739, 25745960), or
Organizing Secretary, Dr.Suresh Gupta (9868219240, 2515265, 25917591,
Email: drguptasuresh@yahoo.co.in)
Department of Pediatrics, Sir Ganga Ram Hospital, Rajender Nagar, New Delhi – 110 060.

It is decided to reactivate medico-legal cell of IAP and start membership drive for this much awaited cell of IAP. The life membership of the cell is Rs 750/-

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QUESTIONS AND ANSWERS

Q.No.1. I want to know what kind of medication can be given for post-operative analgesia for an infant of 1-2 months age? For example: following cleft lip repair. I want to know dosage per kg body weight and frequency of administration.

Dr.M.Venkateswarlu,
Ongole, Andhra Pradesh.

A.No.1. Analgesia or pain relief can be of two types – pre-emptive or balanced. Pre-emptive analgesia involves giving an analgesic agent prior to the onset of pain. Balanced analgesia involves pre-emptive pain relief and provision of continuous relief post operatively as well.

The following concepts are erroneous:

1. It is dangerous to provide pain relief for newborns and infants.
2. It is unnecessary to provide pain relief for newborns and infants.

A pain free child is a happy child and the joy of the parents knows no bounds when they see their child free of pain and discomfort.

Cleft lip surgery:

Paracetamol

Before surgery (on the operation table) - rectal suppository – 30 – 40 mgs / kg as a loading dose followed by 15 – 20 mg / kg / 6 hrly. Suppositories are commercially available in two strengths – 80mgs and 170 mgs.

After surgery - Once oral feeds have been commenced, paracetamol can be given as syrup orally. If paracetamol suppositories are not available, through an 8 size feeding tube, syrup can be injected into the rectum.

Infraorbital nerve block can be given just before or at the end of surgery.

For the night of surgery –

Trichlofos at a dose of 50 to 100 mg/kg can be given orally for sedation.

Cleft palate repair:

Pain relief can be provided with:

1. Rectal paracetamol at the start of surgery
2. Local infiltration with 0.25% bupivacaine during the surgery
3. Trichlofos sodium 50 to 100 mg/kg for sedation on the night of surgery.
4. Morphine (10 to 20 µgm/kg/hr) or Fentanyl (1 to 4 µgm/kg/hr) infusion after surgery. Continuous monitoring by trained nurses is mandatory during the infusion.

Paracetamol:

Paracetamol is the non-opioidanalgesic most commonly used in infants. In lower doses it is antipyretic and in higher doses it is a very good analgesic. It should be regarded, as the first line of agent for postoperative analgesia in infants and it is quite safe in newborns also. The traditionally recommended dose of paracetamol has probably been too conservative. Currently the maximum oral dose of paracetamol is 15 mg/kg PO every 4hrs. Rectal loading dose is 30 to 40 mg/kg followed by 15 to 20 mg/kg PR/PO every 6hrs. Total daily dose should not exceed 100 mg/kg/day in infants and 60mg/kg in neonates. The peak blood level of paracetamol occurs at 60 to 120 minutes. So a loading dose should be given at the start of surgery.

Infraorbital nerve block:

The infraorbital nerve is the termination of the maxillary nerve, which is a branch of the fifth cranial nerve. It emerges through the infra orbital foramen and its branches supply the upper lip

and mucous membrane along the vermilion border. The nerve can be blocked at the start of the surgery (preemptive analgesia) or at the end of the surgery and it can be combined with the other analgesics (balanced analgesia). The infra orbital ridge of the maxillary bone is identified and infraorbital foramen palpated. A 26-gauge needle is advanced and after careful aspiration 0.5 to 1ml of 0.25% bupivacaine is injected.

Conclusion

With experience it will be possible to differentiate the behavioral responses of young children from various causes namely pain, hunger, anxiety or fear. Comforting measures such as being cuddled, parental presence, a favourite toy or a pacifier can be invaluable tools to enhance the effects of the other analgesic agents.

Recommended readings:

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Dr.S.Ramesh MD, DA.
Chief Anesthetist,
Kanchi Kamakoti CHILDS Trust Hospital
Chennai – 34

Q.No.2. Kindly provide me information regarding queries in A.R.V. Post exposure schedule. If a patient fails to take any dose during post exposure prophylaxis (0, 3rd, 7th,14th, 28th, 90th day), shall we have to repeat whole schedule? Is there any alternative schedule for it?

Dr.P.Venkateswarlu,
Visakhapatnam, Andhrapradhesh.

A.No.2. "If anybody misses any dose of 'Essen Protocol for Rabies Prevention', he should continue the rest of the doses as per schedule taking missed dose immediately as per his/her convenience. Suppose his schedule is 1,4,8,15 & 31st March and he failed to take the dose of 4th March and he realize it that he missed a dose on 6th March, he should take the day 3 dose immediately on 6th March keeping the rest of the dose as per schedule. But suppose after missing the dose of day 3 he reported to a doctor on day 9 for the same dose he will take that dose immediately. The next dose, which was due on 8th March ie, the 3rd dose, he has to take on 12th March. But the 4th & 5th dose have to be taken as per schedule. So he need not follow a new schedule and the decision will be to complete the doses as practically as possible. We have to try to finish the number of doses as close to the schedule as possible."

Dr.Tapan Kr Ghosh,
West Bengal

Q.No.3. A 15 months old baby, a doctor's son, was given MMR subcutaneously. A minute after that injection, baby had collapsed. Immediately O_2 and IV line were started. When I visited at 10th minute, baby had cyanosis, bradycardia and occasional respiration. Immediately, I had started Ambu ventilation. After few minutes of Ambu ventilation. I have intubated. After ½ hour baby was given PPV using Boyle's apparatus. As there was no spontaneous respiration even after 2 hours, baby was taken to tertiary hospital and put on ventilator. One hour after that baby had spontaneous breathing and was weaned from ventilator. By 12th hour baby became normal. Parents had noticed few drops of blood oozing out of the injection site. What could be the cause of this respiratory arrest?

Dr.K.Thinakaran,
Salem, Tamilnadu.

A.No.3. From the description, the episode looks like a rare anaphylaxis in view of cyanosis, bradycardia and occasional respiration and collapse after a minute of MMR vaccination. The fact that immediate measures aimed at CPR have

yielded reestablishment of spontaneous respiration, improvement in heart beat and restoration of colour even at the 10th minute have helped to a large extent in recovery also are in favour of an anaphylaxis only. However the necessity to have the baby in the ventilator for about 12 hours warrants further clinical investigation. What was the x-ray chest finding prior to or during ventilation?

Was an ECG monitoring done? What was the ABG finding? Was there any electrolyte imbalance? Slight oozing of blood following subcutaneous infection also seems to be rare and obviously the antigen could not have gained IV access. If all other parameters evaluated are normal, I would still vote in favour of a rare anaphylaxis. It is worthwhile reporting this case in detail. Mild anaphylaxis following MMR vaccine revived by adrenaline administration has been reported by Dr.Nitin K Shah a few years ago from Mumbai. Details can be obtained from him and published simultaneously with this case report. For whatever reason it may be, this child should not risk a 2nd dose of MMR in my opinion.

Dr.A.Parthasarathy,
Retd. Senior Clinical Prof. of Pediatrics,MMC,
Deputy Superintendent, ICH & HC, Chennai.
Chairman, Immunization Committee

NEWS AND NOTES

PEDINEUROCON-2003
5th NATIONAL NEUROLOGICAL CONFERENCE &
31st RAJASTHAN STATE IAP CONFERENCE-2003
HOST: RAJASTHAN STATE BRANCH – IAP

A three day conference is being organized on 7-9th Nov 2003 at Pink City Jaipur

Highlights: Core group meeting on development of protocols for common pediatric neurological illnesses.

Workshops on EEG, Neuroimaging, Electromyoneurodiagnosis

Guest orations, Poster presentations, Award papers, Panel discussion

Registration Fee	Up to 30 June'03	31 Aug'03	6 Nov'03	Spot
IAP Member	Rs 700	Rs 900	Rs 1200	Rs 1500
Non IAP Member	Rs 800	Rs1000	Rs 1300	Rs 1600
Assoc. Member	Rs 500	Rs 700	Rs 1000	Rs 1500
PG students	Rs 500	Rs 700	Rs 1000	Rs 1500

Fee for each one day workshop is Rs 1, 000 BESIDES REGISTRATION

Send your demand drafts in favor of PEDINEUROCON-2003 payable at Jaipur.For

Further details please contact Dr H S Bhasin, Organizing Secretary Pedineurocon-2003

Secretariat: 476A/5 Vyas Marg, Raja Park, Jaipur 304002, Ph 0141- 2621962

Email: pedineurocon2003@hotmail.com