*IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*
*e-ISSN: 2278-3008, p-ISSN:2319-7676. Volume 8, Issue 1 (Sep. – Oct. 2013), PP 49-62*
*www.iosrjournals.org*

# "Enteric Manifestations Management, Introspection."

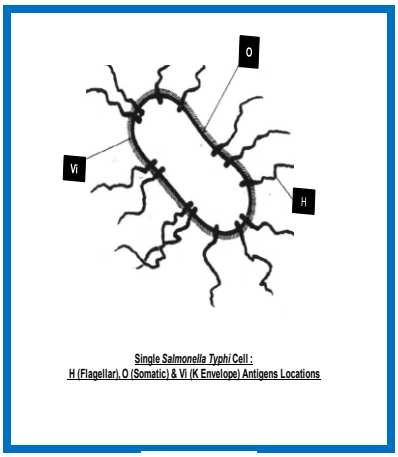
Dr.Anil K. Sahni
*M.S, F.I.C.S., Advanced D.H.A. Surgery Department Co-ChairMan CME,CPD,LLL Programmes VCSG Govt. Medical Sciences & Research Institute Srinagar (Garhwal) – 246174 Uttarakhand India.*

***Abstract*: INTRODUCTION:** *Commonly Prevalent Clinical Problem, Enteric Infections Are Caused By Variety Of Organisms Of Variable Strains, Virulence, Pathogenecity, Epidemiolgy & Geographical Distribution.'Salmonellosis' Caused By Different Salmonella Sp.Changing Species/SubSpecies Strains Variety & Their Sensitivity To Anti-Biotics, Debilitating Diseases, Malignancy, HIV, Immuno-Compromised Status Render Difficult Disease Control, Necessitates Discrete Surgical Observation, Intervention, In Disease Process Variable Clinico-Pathological Manifestations.*
***AIMS/OBJECTIVES :*** *Summarizing Various Aspects Of Comprehensive, "Management GuideLines Plan", Practically Acceptable In Available Resources Circumstances, Achieving Maximal ResultOutcomes,Grouped As Medical Management Methodology,Non-Surgical /Minimally Invasive Conservative Regime & Surgical Management.*
***METHODS:*** *The Varieties Of Clinico-Pathological Manifestations Variants Studied As: CATEGORY(A); Fever,Pain, Inflammation Of Terminal Ileum & Adjoining Viscera. CATEGORY (B); Includes Almost All Cases Of Enteric Perforation Peritonitis, Of Different Disease Duration, In Varying Clinico-Pathological Stages & Associated Toxicaemia.*
***RESULTS:*** *"Overall Treatment Result Outcome Determinants" Include;. Appropriate Antibiotics In Adequate Dosage,Duration Monitored By Peritoneal Aspirate, Blood C&S Etc, Properly Timed Appropriate Surgical(Non/Minimally Invasive/ Open) Procedures, In Appropriation Of GC,Septicaemia Parametres. Associated Medical Problems,Pt.s GC, Type & Severity Of Infection.*
***CONCLUSION: Salmonellosis*** *Manifestations, Amongst Commonest Clinical Practice Dilemmas, Demand Discrete Clinico-Investigatory Assesment For Implementing The Needed ' Treatment Plan' For Maximal'Over All Result OutCome', In Discussed Variable Circumstances.*
***KEY WORDS:*** *1.Enteric (Typhoid) Infections;Epidemiology, Distribution*
*2. Severity Of Infections;? Changing Strains, Systemic Complications*
*3. Medical Therapy Appropriation*
*4. Surgical Intervention;Treatment Modalities Discretion.*

## I.'INTRODUCTION'

'Enteric Infections' Disease Process, Need Careful Clinico-Investigatory Observartion & Timely Discrete Surgical Intervention.

**'Salmonellosis'** Caused By: Salmonella Sp.(Rod-shaped Gram-Negative Enterobacteria) Usually Manifests As:1.Typhoid, Paratyphoid fever ( S.typhii, S.paratyphhi) 2. Enteritis (S.Enteridis) 3.Extra-Intestinal Metastatic & Non-Metastatic Spread eg Cholecystitis Hepato-Biliary, CVS, CNS Involvements, Surgical Wound Infections.



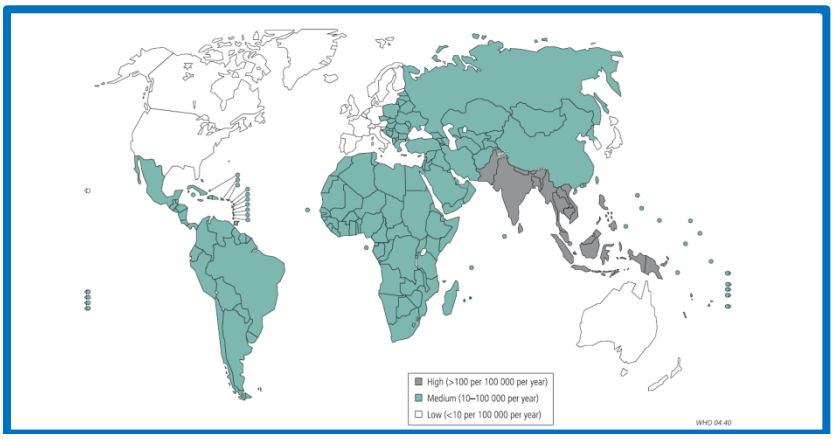

**[Figure-1]**

**Bacteriology:** Culture Characteristics: **Serotype: D** Group Of Salmonella, Gram-negative, Rod Non-spore, Flagellate. Antigens,Located In The Cell Capsule; H (Flagellar Antigen),O (Somatic Or Cell Wall Antigen),Vi (Polysaccharide Virulence)
**Diagnosed;**By Variably Different Titres Of **"Widal Test"**, By Calibrating Endotoxin Levels & A Variety Of Plasmids.
**Resistance;** Live 2-3 weeks in water,1-2 months in stool. Die out quickly in summer. Resistance To drying and cooling Render Authenticity Of "Widal Test".
**Emerging Gram-Negative Enteric Infections Include:** Vibrios; Vibrio Cholera, Non-O1 V Cholerae (Excluding V Cholerae O139), Vibrio Parahaemolyticus, Vibrio Vulnificus, Nontyphoidal Salmonella Species, Shiga Toxin–Producing Escherichia Coli(STEC), Campylobacter, Yersinia Enterocolitica, Unusual Enteric Gram-Negative Bacteria; Aeromonas Species-Aeromonas Caviae (Predominant), A.Hydrophila &A Veronii, Plesiomonas Shigelloides & Other Mixed Sp.Variants.[1,2,3]

**EPIDEMIOLOGY:Continues To Be A Global Health Problem,**
- Areas With A High Incidence Include Asia, Africa And Latin America
- Affects About 6000000 People With More Than 600000 Deaths A Year, 80% In Asia.
- Sporadic Occur Usually, Sometimes Have Epidemic Outbreaks.With An Estimated 16–33 Million Cases Of Typhoid Fever Annually Resulting In 216,000 Deaths In Endemic Areas,

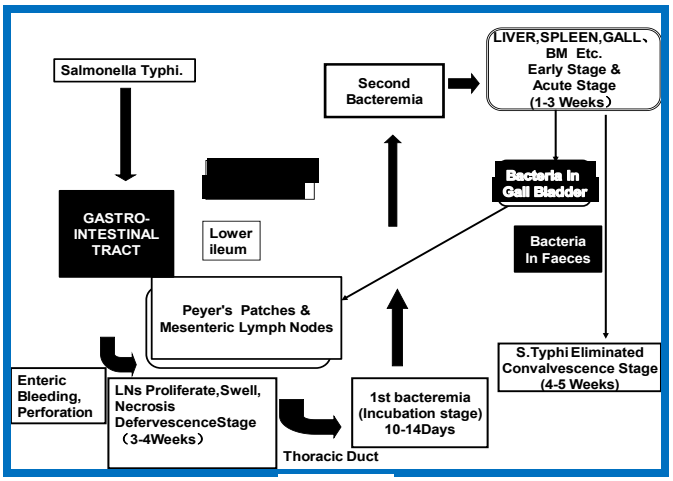
The **World Health Organization** Identifies Typhoid As A Serious Public Health Problem.Its Incidence Is Highest In Children And Young Adults Between 5 And 19 Years Age.Control Of Infection Has Been Achieved In Europe And North America By Effective Public Health Measures,
But Africa, South East And South Central Asia, Continue To Bear The Burden Of The Disease, Principally Because Many Communities Still Fall Short Of Standards For Drinking Water, Hygiene And Sanitation.

**The Incidence Of Typhoid Fever In The United States,** Has Markedly Decreased Since 1920s(>35,000 Cases),To Latest (Approximately 400 Cases, Mostly Traveller To Endemic Areas), As Reported Annually.




**[Figure-2]**
**GEOGRAPHICAL DISTRIBUTION(PREVALENCE)**
**'WHO' Report**

**Source Of Infection:**Body Discharges From Incubation(More In 2~4 Weeks After Onset & About 2~5% For >3 Months.)
**Chronic Carrier** eg *Typhoid Mary*
**Transmission:**Fecal-Oral Route,Close Contact With Patients Or Carriers, Contaminated Water And Food, Flies And Cockroaches.
**PATHOGENESIS:**Gastrointestinal Tract Host-pathogen Interactions,
WithThe Amount Of Bacilli Infection ($>10^5$bacteria),Ingested Orally Crossing Stomach Barrier (Some Eliminated), Enter The Small Intestine,Penetrate The Mucus Layer, Enter Mononuclear Phagocytes Of Ileal Peyer's Patches And Mesenteric Lymph Nodes, Proliferate In Mononuclear Phagocytes.
**Spread To Blood**:**Initial Bacteremia** (Incubation Period),Enter Spleen, Liver And Bone Marrow(Reticulo-endothelial System)-Further Proliferation Occurs, Resultant
Large Bacterial Load Enter Blood Again,**Second Bacteremia**, Followed By Recovery.




**[Figure-3]**

**'SALMONELLOSIS' LIFE-CYCLE'**

**CLINICAL MANIFESTATIONS:**

**Incubation Period: 3～60 Days(7～14).**

**THE INITIAL PERIOD (EARLY STAGE);** First Week,Insidious Onset,Fever Up To 39~40$^0$c In 5~7 Days,Chills, & Or Other Constitutional Symtoms.

**RECRUDESCENCE;** Is Reappearance Of Clinical Manifestations, Less Severe Than Initial Episode.In Temperature Recrudesce,Temperature Starts To Step Down But Remains Abnormal, In Period Of 2-3 Weeks,Persisting 5~7 Days,Before Normalizing.

Seen In Patients With Short Therapy Of Antibiotics.

**RELAPSE;**Serum Positive S.Typhi After 1～3 Weeks Of Temperature Down To Normal, Symptom And Signs Reappear Indicating Incomplete Eradication Of Bacteria, Some Times Relapses Occur More Than Once.

**THE FASTIGIUM STAGE;**Second And Third Weeks, Sustained High Fever

(Partly Remittent Or Irregular),Lasting 10～14 Days.

**Gastro-intestinal Symptoms,Neuropsychiatric Manifestations,**

**Circulatory System:** Relative Bradycardia Or Dicrotic Pulse, Toxic Myocarditis

(Seen In 2-3 Weeks), Usually Severe Toxemia.

**Splenomegaly、Hepatomegaly:** Toxic Hepatitis(Common1-3 Weeks,

ALT Elevated,Get Better In 2~3 Weeks).

**Bronchitis, Bronchopneumonia:** Seen In Early Stages.

**Roseola :**30% Cases, Maculopapular Rash,Faint Pale Color, Slightly Raised, Round Or Lenticular, Fade On Pressure, 2-4 Mm In Diameter, Less Than 10 In Number On The Trunk, Disappear In 2-3 Days.

[27,28]**Changing Species / SubSpecies Strains Variety & Their Sensitivity To Anti-Biotics, Presence Of Debilitating Diseases, Malignancy, HIV Immuno Compromised Status Render 'Salmonellosis' Control Difficult. Discrete Surgical Observation, Intervention Are Necessitated, In Several Differently Variable Clinico-Pathological Manifestations Of Disease Process.** [4,5,6]

**DIAGNOSIS**

**Laboratory Findings**

**RoutineExaminations;WBC-**Normal OrDecreased,Leukocytopenia Esp.Specially Eosinophilic Corresponding To Diseases Improvement & Relapse,**Low Platelet Count.**

**Bacteriological Examinations;**

**Blood Culture:** Most Commonly Use, 80~90% Positivity During The First 2 Weeks,50% In 3rd Week,Not Easy In 4th Week, Re-positive When Relapse And Recrudescence.

**Bone Marrow Culture:** The Most Sensitive Test,Specially In PreTreated Patients.

**Urine And Stool (Rectal Swab) Cultures:**Increase The Diagnostic Yield,But Positive Less Frequently. Stool Culture Better In 3~4 Weeks.**Elisa Urine Test.**

**Fluorescent Antibody Study:** For Substances Specific To Typhoid Bacteria.

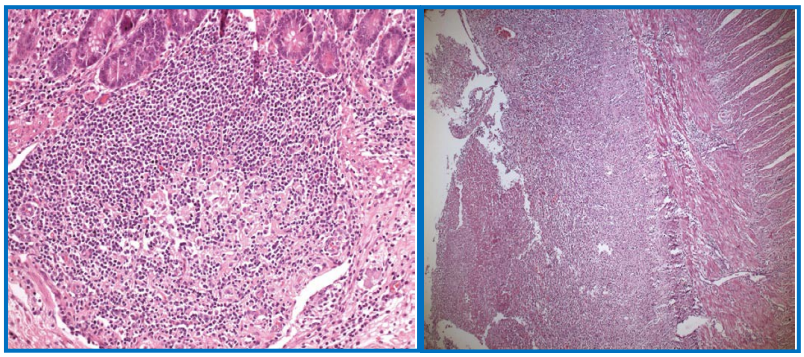
**Duodenal String Test:**Bile Culture,Esp.Useful For Carriers Diagnosis.

**Rose Spots:** Not Used Routinely.

**Peritoneal Aspirate C&S: Simple, Safe, Comparatively Easy To Perform With Better Specificity,** Due To Consideration Of Complete PeritonealEnvironment From InitialContamination By Predominant Facultative Gram-Negative Organisms eg *Escherichia Coli* And Klebsiella, Eventually Obligating Anaerobes From Colon As Dominant Bacteroides Species.
**Serological Tests (Widal Test):** Five Types Of Antigens:Somatic Antigen(O), Flagella(H) Antigen And Paratyphoid Fever Flagella(A,B,C).
Antigen.Antibody Reaction Appear During First Week, 70% Positive In 3~4 Weeks
And Can Prolong To Several Months.
In Some Cases, Antibodies Appear Slowly, Or Remain At A Low Level,
While In 10~30% Cases,Dont Appear At All.
**Interpretations:"O" Agglutinin Antibody Titer ≥1:80 And "H" ≥1:160 Or**
**"O" 4 Times Higher Supports A Diagnosis Of Typhoid Fever.**
**"O" Rises Alone, Not "H" -** Early Of The Disease.
**Only "H" Positive, But "O" Negative -** Often Nonspecifically Elevated By Immunization Or Previous InfectionsOr Anamnestic Reaction
**Antibody Level Maybe Lower In Early Used Antibiotics Cases.**
Some Cross Reaction Between Group "D" And "A".
False Positive In Some Infectious Diseases.
Some Positive In Blood Culture , But Negative In Vidal Test.
**'Vi" (1:40) Often Useful For Carrier Diagnosis.**
**Molecular Biological Tests**:DNA Probe Or Polymerase Chain Reaction (PCR); Identification Of Salmonella Typhi DNA By PCR With 100% Sensitivity And Specificity Is Promising Gold Standard If Affordable. [7,8,9]
**DIFFERENTIAL DIAGNOSIS:**Viral infections, Malaria, Leptospirosis, Epidemic Louse-Borne typhus, Tuberculosis, Septicemia of Gram-Negative Bacilli,Typhus, Recent Swine Dysentery Infections Etc.
**PARATYPHOID FEVER A,B,C:**Caused By Salmonella Paratyphoid A,B,C.Respectively. Similar To Typhoid Fever In Epidemiology, Pathogenesis, Pathology,Clinical Manifestations, Diagnosis, Treatment And Prophylaxis.
**ParaTyphoid A,B:**Incubation Period 2~15days, In General, 8~10 Days, Milder In Severity Fewer In Complications,Better In Prognosis, Relapse More Common In Paratyphoid A,Treatment Same As In Typhoid Fever.
**ParaTyphoid C:** Always Sudden Onset, Rapid Rise Of Temperature,Cl.Presentations -- Septicemia,Gastroenteritis And Enteric Fever,Complications--Arthritis, Abscess Formation, Cholecystitis, Pulmonary Complications Are Common,Intestinal Hemorrhage And Perforation, Less Common ThanTyphoid Fever. [61,62]

## COMPLICATIONS

**(1)INTESTINAL HEMORRHAGE;**Commonly Appear During 2-3 Weeks, Usually Prescipitated By Unsuitable Food, Diarrhoea Etc. Mild And Serious Bleeding(In 2~8%), Ensuing Shock Is Followed By Dark Or Fresh Blood In The Stool.
**(2)INTESTINAL PERFORATION;** [29,30,31,32,33]
**Pathogenesis:**
**Essential Lesion;** Proliferation Of RES (Reticuloendothelial System),
Specific Changes In Lymphoid Aggregates Of Peyer's Patches Of The Terminal Ileum) And Mesenteric Lymph Nodes, 'Typhoid Nodules'Formation.
**Most Characteristic Lesion;** Mucosal Ulceration In The Region Of The Peyer's Patches Of The Small Intestine (Extending From The Lamina Propria To The Submucosa) **InStages:**
**Hyperplasia (1st Week);** Swelling Lymphoid Tissue And Proliferation Of Macrophages.
**Necrosis (2nd Week);** Lymph Nodes Or Solitary Follicles Necrosis.
**Ulceration (3rd Week);** Necrotic Tissue Shedding And Ulcer Formation Leading To
**Intestinal Hemorrhage, Perforation .**
**Healing (From 4th Week);** As Ulcer Healing ,If No Cicatrices No Contraction.
**The Process Leading To Tissue Damage Is Probably Multifactorial, Involving Both Bacterial Factors And Host Inflammatory Response, With The Significant 'Treatment Appropriation Factor'.**
**The Sanarelli-Shwartzman's Reaction**,1937, Provideds Insight To Basic Mechanism. **Gut Macrophages Activation** Occurs By Salmonella typhii **Directly** By Toll Like Receptors **Or Indirectly** Via Antigen Presenting Cells.
**The First Gut Exposures** Sensitizes The Macrophages, Initiating Release Of Damaging Cytokines Such As Tumor Necrosis Factor-Alpha. **At Second Exposure**.Pathological Changes Are Not Just Restricted To Perforation Sites.



**[Figure-4]**

**TYPHOID LESIONS HISTOPATHOLOGY**

**A:** Typhoid nodule;Macrophages Containing Bacteria, Red Blood Cells, And Nuclear Debris From Small Nodular Aggregates In Peyer's Patches

**B:** Typhoid Ulceration

**The Diseased Gut** Is Characterized By Diffuse Nonspecific Enterocolitis With Changes Of Intestinal And Mesenteric Lymphatic Tissue. Acute And Chronic Inflammatory Cells Are Involved With Predominance Of $CD68^{+}$ Leucocytes (Macrophages) , And $CD3^{+}$ T Lymphocytes At Perforation Sites.

**[Figure-5] INTESTINAL PEYER'S PATCHES**

**Reports Of Peyer's Patches Involvement, In TP Is Debated, As Current Evidences Suggest The Mechanism Of Intestinal Injury Complicating Enteric Fever To Be Immunologically Mediated, Through Release Of Cytokines From Macrophages.**

**Site:** Terminal 40 Cm Of Ileum - 72%-78% ; Jejunum, Caecum, Colon And Gallbladder To Lesser Degree, Rarely Duodenal And Appendiceal Perforations Cases.

Perforations May Be Multiple (3%-40%)Especially In Younger Children.

**Clinical Features**:Common During 2-3 Weeks, Abdominal Pain,Diarrhea, Intestinal Bleeding. May Precede Ensuing Charactertic Perforation Peritonitis & Associated Features Of Varying Toxiaemia.

Non-Perforation Peritonitis - About 5% Cases.

Studies Report Male:Female Ratio 2.5 – 4(Reason Obscured)

Hepatosplenomegaly Common(As Significanct TP Predictor UnClear).

**Dx:** X-ray -Free Gas Under Diaphargm,USG-Free Fluid & Suggestive Lab. Invs.

**Prognosis**: TP Occurs In 0.6% - 4.9% To 10%-33% With About 25% Mortality.

Fully Developed Immune System In Prevalence Age Group 5 - 30 Years, Supports Less Morbidity & Mortality, Compared To Paediatric Age Group. [34,35,36,37,38,39]

**(3)OTHER COMPLICATIONS;** Cytokines And Other Mediators Released By Immune Cells In Response To Infection Cause Local And Systemic Inflammation. The Cytokine Response With Potential Of Self-Perpetuation (Even After Successful Control Of Infection Source) Lead To Systemic Cellular Injury And Multiple-Systems Organ Failure,eg **Toxic Encephalopathy.,Hemolytic Uremic Syndrome, Acute Cholecystitis, Meningitis,Nephritis,Toxic Myocarditis** Etc.

## II.'AIMS/OBJECTIVES'

By More Than (2) Decades, MultiCentric Clinical Observational Study,

In The Variable Resources Availability Circumstances, Various Aspects Of Comprehensive**"Management Guideline Plans",** Practically Acceptable In Prevailing Situations, Achieving Maximal Result Outcomes, Are Summarized As -

**(1)Medical (2) Surgical**

**(3) Non-Surgical / Mininimally Invasive Management Methodologies.**

## MEDICAL MANAGEMENT METHODOLOGY

With Emphasis Upon Meticulous Use Of Appropriate Anti-Microbials Preferably In Accordance With C&S (Blood, Urine +- Peritoneal Aspirate) & Needed Intensive Supportive Measures.

**Definitive Treatment Of Typhoid (Enteric) Fever** Is Based On **'Susceptibility'**.

As A General Principle Of Antimicrobial Treatment, **'Intermediate Susceptibility'** Should Be Regarded As **Equivalent To Resistance**.

Between 1999 And 2006, 13% Of *S Typhi* Isolates Collected In The United States Were **'Multidrug Resistant'.** A Significant Number Of Strains From Africa And The Indian Subcontinent Are **MDR.** South Asia, East Asia, Eastern Europe, Middle East, Sub-Saharan Africa,South America, Southeast Asia Or Unknown **'Geographic Origin'**, Have **'Demonstrable Variations' Of Strain,Severity & Resistance.**

**Nalidixic-Acid-Resistant *STyphi* (NARST) Strains**(Ciprofloxacin Resistant), Either Chromosomally Or Plasmid Encoded, Are Observed In Asia.[10,11,12,13]

**TYPHOID:ANTI-MICROBIAL THERAPY**[14,15,16,17,18,19,20]

**Antipyretics;**The Pyrexia Can Be Managed WithTepid Baths And Sponging. Salicylates And Antipyretics Should Be Avoided, Because They Cause Severe Sweating And Lower The Blood Pressure.

**TABLE-1**

**TYPHOID:ANTI-MICROBIAL THERAPY**

**(Drug Dosage Route, Duration In Days, Mg/Kg/Day Schedules)**

| **FIRST-LINE** | **SECOND-LINE** | ***OTHER ANTIBIOTICS*** |
|---|---|---|
| **Chloramphenicol** 500 mg Qid 50 mg/kg in Oral, IV antibiotics: 4 doses<br>**Trimethoprim**- 160/800 mg bid 4-20 mg/kg: Oral, IV Sulfamethoxazole In 2 doses<br>**Ampicillin /Amoxycillin** 1000-2000 mg qid Oral, IM, IV 50-100 mg/kg:In 4 doses | **Ciprofloxacin** 500 mg bid/200 mg bid Oral/IV antibiotics: for 10-14 days<br>**(Fluoroquinolones)**<br>**Norfloxacin** 400 mg bid for 10 days Oral<br>**Pefloxacin** 400 mg bid for 10 days Oral, IV<br>**Ofloxacin** 400 mg bid for 14 days Oral<br>**Levofloxacin** 500 mg bid for 14 days<br>**Cephalosporins Ceftriaxone** 1-2 gm bid 50-75 mg/kg: in IM, IV 1-2 doses<br>For 7-10 days<br>**Cefotaxime** 1-2 gm bid 40-80 mg/kg: IM, IV in 2-3 doses for 14 days<br>**Cefoperazone** 1-2 gm bid 50-100 mg/kg: IM, IV in 2 doses 14 days<br>**Cefixime** 200-400 mg od/bid Oral10 mg/kg: in 1-2 doses for 14 days | ***Aztreonam** 1 gm/bd-qid 50-70 IM* mg/kg: 2-4 5-7<br>**Imipenem** IV<br>**Azithromycin** 1 gm OD 5-10 mg/kg:1 5 Oral |

**Note:**The Combination Of Azithromycin And Fluoroquinolones Is Not Recommended, Because It May Cause QT Prolongation And Is Relatively Contraindicated.

**'NHS' Recommends : Medications In Accordance To Blood Culture.**

**Supportive Measures;** Are Important In The Management Of Typhoid Fever, Such As Oral Or Intravenous Hydration, Tepid Baths And Sponging And Appropriate
Nutrition And Blood Transfusions, As Need.[21]

**Therapeutic Strategies Will Have To Take Into Account The Local Antibiotic Sensitivity Patterns Of *S.Typhi* While Refining Treatment.** [23]

**Role Of Gluco-Corticoids;** Reported Studies, Advocating Gluco-Corticosteroid Use(Conventional Dosage Regime), For Severe Typhoid Disease Management,
Especially For CNS Symptoms, Severe Toxicaemia & Resultant Profound Septicaemia Patients Category.
Although,Reported Significant CFR Improvement & No Adverse Effects During Wide Experience Of Corticosteroid Treatment, Except The Potential For Masking Intestinal Perforation, Corticosteroids Use Should Be Best Reserved For Severe Illness Patients .

**During The Course Of Present Study, A Group Of Large No.Of Patients, Manifesting Very Resistant Post-operative Severe Hyperpyrexia, Have Been Managed With Minimal Dose Steroids.The Comparative Evaluation Analysis, In Regards To Repair Leak, Wound Dehiscence & Other Morbidity Factors With Mortality & OverAll Result OutComes ParaMetres,Support The Judicious Discrete Use Of Steroids.**[22]

## TYPHOID CARRIERS' MANAGEMENT

**'Chronic Carrier':** Patients Who Continues To Discharge *S. Typhi* In Either Urine Or Stool For Longer Than 1 Year. Treated By - Ampicillin 100mg/Kg, Tid /Qid Oral,
Amoxycillin+ 30 Mg/Kg Oral, Probenicid Co- Trimoxazole 4-20mg/Kg Bid Oral, Ciprofloxacin 1500 Mg Bid Oral, Norfloxacin 800 Mg Bid Oral, For Needed Durations.

**Long-Term Suppressive Antimicrobial Therapy** Is Considered For Patients With Persistent Carriage With No Identified Anatomic Abnormality, Or Relapse After Cholecystectomy.
**In Cases Of Anatomic Abnormality (eg. Chronic Cholecystitis ,Biliary Stones),** As Carrier State Eradication Is Non-Achievable, By Antibiotic Therapy Alone, Surgical Correction(Cholecystectomy) Is Mandatory, As Eliminates Carrier State In 85% Cases & Is Specially Recommended For Professional Occupations eg Food Handlers And Health Care Providers.
**An Effective, Well-Tolerated Typhoid Vaccine Could Help Control Both Endemic And Epidemic Disease.**[24,25,26]
**Reported Safe Yet Cautious Co-Administration,**With Other Vaccines Relevant For International Travellers(Yellow Fever, Hepatitis- A),Including Live Vaccines Against Polio, Cholera Or Measles, Mumps And Rubella (MMR) Combination & Routine Childhood Immunization Programmes Vaccines.

**TABLE-2**
**'TYPHOID VACCINES'**

| VACCINE | ROUTE , DOSAGE | REVACCINATION | OTHER DETAILS |
|---|---|---|---|
| **(I.) Killed,Whole Cell; Phenol-Inactivated Vaccine** (Shot) | Subcutaneous 0.5 ML, 2 Times(1-4 Weeks Apart), At Least 2 Weeks Before Travel | 1-2 Years, (Depending Upon Risk). | First Available,Still In Use In Some Developing Countries, Due To High Reacto-Genecity (Fever & Systemic Reactions), Needs Replacement By Newer Availabilitie(WHO). |
| **(II.) Live; Attenuated *S. Typhi* Strain Vi CPS** (Ty 2 S -Purified Vi capsular Polysaccharide). | Subcutaneous /Intramuscular, 0.5 ml, 7 Days Before Travel. | 2-3 years, (Depending Upon Risk). | First Licensed; 1994,USA, Recommended For Age >2 Years, Storage emperature 2–8 ºc, Minimal Local & No Serious Side-Effects, Safe For HIV Infected Individuals (As Protective Antibodies Induction Is In Direct CorrelationTo CD4 Positive T-Cells Levels.) |
| **(III.) Oral, Live Attenuated, Purified Vi Capsular Polysaccharide Vaccine Ty 21 a** (Chemically Mutated Multiple Genes Ty2 Strain Of S. Typhi Including The Genes For Vi Production). | Oral, Lyophilized Vaccine- (Enteric Coated apsules(>5 Years) Or Liquid Suspension (From 2 Years Age). One Capsule On Days 1,3,5,7 (3 Or 4 Doses Regime Variations US,Canada,Europe), Last Dose At Least 1 Week Before Travel. | 3-5-7 Years, (Depending Upon Risk). | First Licensed; Europe,1983 And USA ,1989. Remarkably Well Tolerated Low Rates Of Adverse Events |

**Safety Precautions:**
**Inactivated Typhoid Vaccine (Shot);**Children >2 Years Age, Severe Reaction To Previous Dose(Severe Allergy To Vaccine Component),Moderate Or Severe Illness At The Scheduled Time(Wait Till Recovery).
**Oral Vaccine;** Swallow(*Not To Chew)* About An Hour Before Meal With Cold Or Lukewarm Drink.
**Each Of These Vaccines Offer 55% To 85% Protection For 3 To 5-7 Years.**
The OverAll Side Effects Are Variable & Not Very Significant.
**Other Vaccines:TAB Vaccine(Inactivated *Salmonella*),**Used For The Second Commonest Enteric Fever In Asia, Caused By ***S. Paratyphi* A,** Reporteded Strong Reacto-Genecity. New***S. Paratyphi* A Vaccine (Composed Of The Surface O-Specific Polysaccharide Conjugated With Tetanus Toxoid),**
Recorded To Be Safe And Immunogenic.
**Vi-rEPA :** New Vi Conjugate Candidate Vaccine Bound To **(rEPA) Non-Toxic Recombinant *Pseudomonas Aeruginosa* Exotoxin A** (ReportedEnhanced Immunogenicity) & Three live attenuated candidate vaccines Are In Evaluation Process.

## III.'METHODS'

Enteric Fever Patients Need Observation, Interference, Intervention By Surgeons,
In Several Differently Variable 'Clinico-Pathological Manifestations',
**The Varieties Of 'Variants' Are Grouped As:**

**"CATEGORY(A)"**

**Includes Clinical Presentations:**Pain In The Lower Abdomen,Similar To Appendicitis,PID,Tubo-Ovarian Diseases Etc.**Clinical History:**Fever;About >3 Weeks Duration,

**Clinical Exam:** Localized Tenderness & 'Signs Of Peritonism'

**Laboratory Investigations** Suggestive Of Salmonellosis, While

**Competent USG** May Reveal Infective, Inflammatory Changes Of Terminal Ileum With Exlusion Of Appendicular, T.O Pathology, PID, Rt.Urolithiasis Crystalluria & Other Causes Of Abdominal Pain.

**The Meticulous Treatment Plan Includes:** Monitored Oral Intake, IV Fluids Supplementation, Proper AntiBiotics Including AnAerobs In Adequate Dosages,Duration, Antipyretic,Anti-Inflammatory,Analgesic Combinations, Proper AntAcid As Needed(?APD Status ? Nausea, Vomittings),B-Complex & Other Nutritional Supplements.

**Majority Of These Patients Recover Less Then A Week's Time,** Discharged With Domiciliary Tratment & FUC Advise For Review With Suggested Investigations, Till Clinico-Diagnostic Disease Clearance.

The Discussed Category Being One Of The Important Examples Of Proper Timely Dx & Subsequent Methodical Tt. Plan, Avoiding Occurrence Of TP & Variable Complications.

**"CATEGORY (B)"**

**Includes Almost All Cases Of 'Enteric Perforation Peritonitis',**Of Different Disease Duration,In Varying Clinico-Pathological Stages & Associated Toxicaemia, Septicaemia, Shock Status.

**Discrete Pre Operative Assessment,Supported By Intra-Operative Evaluation Retain The 'Decisive Status' For Supportive Therapy Methodology Regime & Or Appropriate Surgical Procedure Performed,** So As To Attain Maximal Result Outcomes, With Minimal Morbidity & Mortality.**After Confirmation Of Diagnosis By,**

**Radio-Diagnosis;**X-Ray Abd (Erect)Including Both Domes Diaphargm:Free Gas Under Diaphargm Signifying Visceral Perforation(+-) Variable Obstruction.

USG Whole Abdomen(Full Bladder);Variable Amount Free Fluid Peritoneum, Intestinal Loops Status & OtherAssociated Pathologies eg Gall Bladder Biliary Diseases Etc.

**Laboratory Investigations;**Widal Test Serology Confrm Various Different Types & Severities Enteric Infection, Blood C&S And **Peritoneal Aspirate C&S**

**(Specimen Obtained From Radio-Dignostic Guided Aspiration & Or Exploratory Laparotomy) C&S Being Important Dx Tools Of Immense Therapeutic Result OutCome Advantage By Minimizing Disease Process Morbidity & Mortality.**

**Concomittantly Performed:**HaemoGram,Urine,Blood Sugar Profile, Renal Function Tests, S.Amylase, Lipase, S.Electrolytes, Needed LFTs, HIV For Aids, HBSAg & Other Available Specific Serolgical Tests.

**In Cognizance With,** Available Cl.History Of Known Medical Illnesses With Previous Tt. Details Etc. & Patient's General Condition, As Recorded Vital Parametres(GC,Pulse, BP, Resp., Temp, Anaemia, Hydration Level Clinicaliy In Consideration Of Urine Out Put ,$SpO_2$ Levels).**Vehement Conservative Measures Immediately Initiated,**

**(Preferably In Well Equipped ICUs) Include:**

**(A)Gastro-Intestinal Decompression:**R.T Aspiation,Continuous Drainage With (2)Hourly Aspiration
Umblical Level Abd. Girth Measurements , ? Lump Monitoring
Needed Manual Removal Of Faeces(MRF), Flatus Tube Etc.
Enemas Are Usually Avoided In Acute Surgical Abdomen Conditions.

**(B) Intensive Fluid Resuscitation :**Correction of Circulating Volume & Electrolyte Imbalance Supplementation Of Fluid Losses By Adequate Rations Of Appropriate Fluids In Consideration Of Vitals Monitoring, Intake/OutPut Charts, S.Electrolytes , Other Laboratory & Electronic Monitors Available.

**(C) Medications:**Appropriate Antibiotics(Broad Spectrum, Aminoglycoside, Anaerob AntiMicrobial Combination) In Adequate Dosge,Duration.In View Of Bacterial Flora, Epidemiology,C&S Reports (Blood, Urine, Peritoneal Aspirate Etc.),Is The Most Important Aspect Of Tt.
Antacids(PPI,H2 Receptor Blockers Etc.)
Analgesic, Anti-Inflammatory & ? AntiPyretics.
B-Complex & Other Nutritional Supplements.

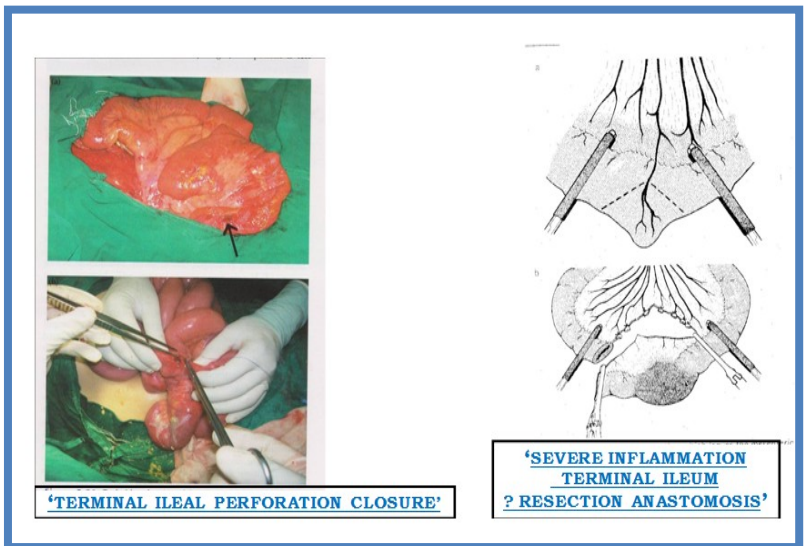
**(D) Other Supportive Measures:**Needed Ventilatory Support: As Monitored By $SpO_2$ Levels,Oxygenation In Different Concentrations, Continuous/Intermittent, Using Different Appliances. Steam Inhalation, Nebulizers:Medications , Chest Physio-Therapy,As Needed.

**Continuous Monitoring of Cardiac, Renal, Hepatic ParaMetres & Needed ManageMent Measures Especially In Pts. With Known Medical Ailments & Tt. Histories.**

**With Supportive Therapy Intiated,**In Colloboration With PreAnaesthetc CheckUp, Prospects Of The Differing Extents Surgical Procedures, Are Meticulously Assessed, Evaluated & Discussed Finalized With Patient / Attendants For Their 'Consent' & Compliances.

**With Discrete PreOperative & Or PerOperative Assessment, Appropriate Surgical Procedure Is Performed Amongst, [51,52,53,54,55,56,57] Exploratory Laprotomy, Perforation/s Closure +- Omental Patch, Ileostomies(End/Loop)Exteriorizations, Resection Anastomosis, Proximal Jejunostomy, Hemicolectomies, Laparostomies & Needed Cholecystectomy Etc.**

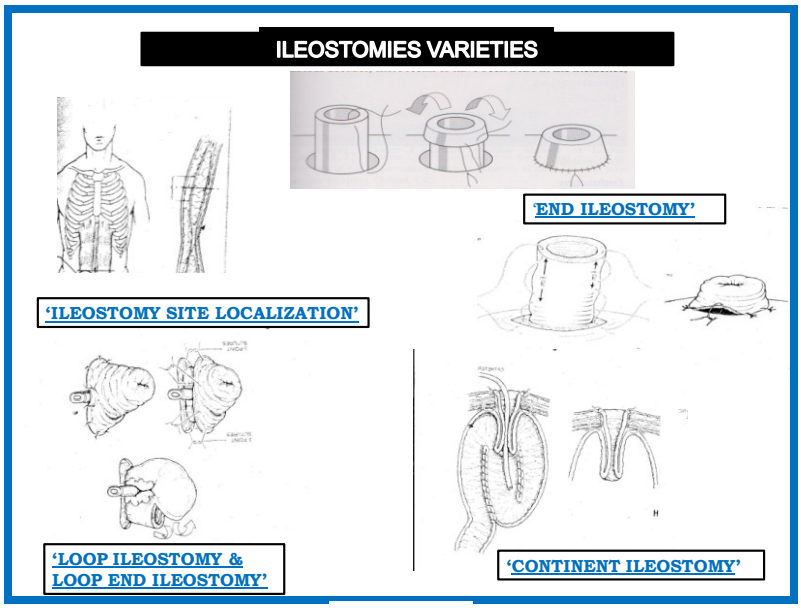
**Exploratory Laprotomy:**Peritoneal Drainage,Peritoneal Lavage With N.S & Betadine, Identification Of Enteric Perforation(Solitary, Usually Found In About 1-2 Feet Of Terminal Ileum) &Closure Along The Longitudinal Axis Of Bowel, Single/Two Layeres Using CatGut/Silk/Vicryl ,Surgical Wound Closure In Layers, Using Vicryl/Prolene & Silk/Skin Staples,With (2) Intra-Peritoneal Drainages,In Flank & Pelvis, Sterile C&D.




**[FIGURE-6]**
**"ENTERIC PERFORATION-SURGICAL PROCEDURES"**

**Ileostomies Of Different Types:** With Subsequent Elective Repairs.
**Ileostomy Indications:** Multiple Enteric Perforations At Different Levels Of Bowels, Rendering Simutaneous Closure Difficult Due To Multiplicity, Sites & Inflammed Infective Bowel Lengths With Jeopardized Viability.
**Loop / Double-Barrel / Tube Ileostomy Has The Advantage** Of Extra-Peritoneal Closure & Intra-Peritoneal Deposition,Without The Need Of II Stage Exploratory Laprotomy, As Needed For End-Ileostomy Cases.

**HowEver, During The Recent Course Of Present Study, Several Case With Variable Lengths & Viability Status Of Bowel, Due To Infection Inflammation Process Status, Have Been SucessFully Treated Avoiding Ileostomy, By Maximal Dosage Regime Of Inj. Ceftriaxone 6-8 Gms /Day & Concomittant Use Of Inj.Oflox;800 Mgms/Day Dosage & Anaerobs Anti-Micobials,Post-Operatively. Recently UseFul Role Of AzithroMycin For Enteric Fever, Has Been Recommended(WHO).**




**[FIGURE-7]**

**"ENTERIC PERFORATION-SURGICAL PROCEDURES"**

**T-Tube Ileostomy For Caecal And Colonic Perforation:** Wedge Resection And Simple Closure(Usually Sufficient For Commonest Occuring Solitary Caecal Perforation),Simple Closure And Ileostomy And Partial Colectomy With Colostomy.

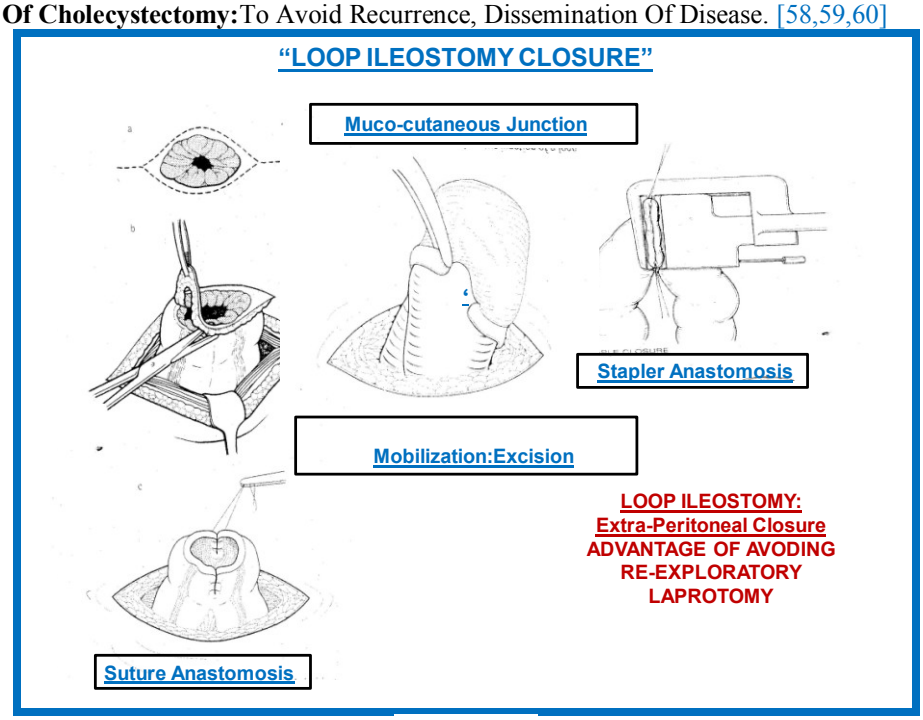
[40,41,42,43,44,45] **In Children:** Anatomically Narrow Terminal Ileum Compounded By Typhoid Enteritis, Cause Additional Challenges To The Security Of Repair.

**The InAdequacy Of Single Operation To Control 'Source Control',** In Patients With Secondary Peritonitis & The Recommended Yet Debated Role Of Ileostomy, As A First Line Operation Is Recommended In Severe Peritoneal Contamination Circumstances. With Advantages Of Enhanced Intestinal Decompression, Early Ileus Resolution & Enteral Feeding With Improved Healing,The Risk Of Re-Perforation Is Further Reduced By Combining Ileostomy With Resection. [46,47,48]

**Laprostomies:**Open/Closed Or Mesh Varieties, Sometimes Performed To Avoid Abdominal Compartment Syndrome(ACS) Etc.

**Laparoscopy:** ?Definitive Role As New Procedure.

**Useful Role Of Cholecystectomy:**To Avoid Recurrence, Dissemination Of Disease. [58,59,60]




**[FIGURE-8]**

**"ENTERIC PERFORATION-SURGICAL PROCEDURES"**

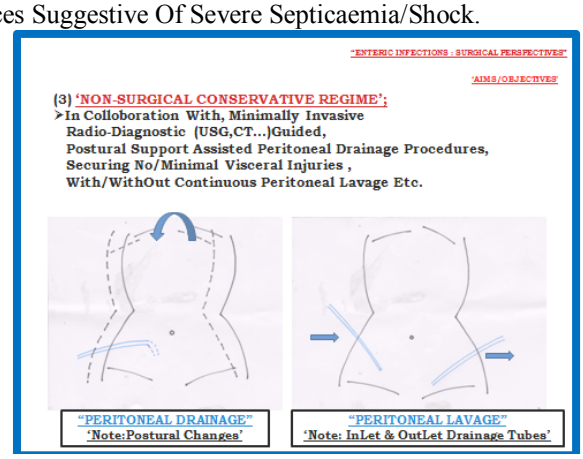
## CONSERVATIVE (NON-SURGICAL) MANAGEMENT METHODOLOGY

**Indications:**Perforation Peritonitis Cases, With Solitary/Multiple Perforations,
With/WithOut Localized Peritonitis Adhesions,Involved Highly Inflammed Bowel Loops Of Different Lengths.

**1.**Poor/ V.Poor G.C,With/WithOut Associated Medical Problems; [49,50]
Uncontrolled ? Labile Status V.High Risk / Not Fit For Surgery.

**2.**Severly Derranged Hydration Status,To The Extent Of Oliguria/Anuria(ARF↔CRF),
Derranged Renal Function Tests Non Revertible By Initial Intensive Fluid Therapy &
Other Measures.

**3.**Clinico-Investigatory Indices Suggestive Of Severe Septicaemia/Shock.




**[FIGURE-9]**

## RADIO-DIAGNOSTIC (USG,CT…)GUIDANCE: POSTURAL SUPPORT ASSISTED, PERITONEAL DRAINAGE PROCEDURES

**With Intensive Cautious Carefully Monitored Supportive Measures** Including Meticulous Medical Therapy,Under Radio-Diagnostic (USG,CT…)Guidance,
Securing No/Minimal Visceral Injuries,Postural Support Assisted, Peritoneal Drainage Procedures, With / Without Continuous Peritoneal Lavage Are Performed Utilizing Wide Bore I.V. Canula / Drainage Tubes,**Peritoneal Aspirate Subjected To C&S, For Including Proper Anti-Microbials In Tt. Plan.** Needed Subsequent Exploratory Laprotomy Safely Planned After The Improvement Of OverAll G.C Of Pt.

**Comparative Statistical Analysis Evaluation Of Discussed Methodology,**
Demonstrated,Comparative Better Result OutComes,In Regards To Mortality & Morbidity,Of Severe Enteric Disease Cases eg Old Enteric Peritonitis,
With Associated Medical Problems.

## IV'RESULTS'

**The Historical LandMark Of 'Chlamphenicol Discovery '1948,** Followed By Gradual Improvement In The Understanding Of The Disease Pathogenesis And Progress In Areas Of Supportive And Surgical Care Led To Decline In Disease Morbidity & Mortality,Of Differing Statistical Extents, In Various Global Regions.

**Review Of Publications** From Available DataBases, From 1960 To 2010, Reveal Gradual But Variable Global Decline, In Case Fatality Rate(CFR) For TP, In Different Parts Of The World, **While The Ever Continuing Controversial Debate** Regarding Operative/Non-Operative Treatment, Has Been Differently Reported In Various Studies. With Improved Mortality Rates, Better Morbidity Indices Achievement,
Is Present Day Need.[63,64,65,66,67,68,69,70,71,72]

**The Inferences Of The Present Study,** A Comparative Statistical Analysis, Based Upon Clinico-Investigatory Assessment & OverAll Result Outcomes, Suggestive, **"Overall Treatment Result Outcome Determinants",** Are Categorized As-

- **Properly Timed Appropriate Surgical(Non/Minimally Invasive/ Open) Procedures,**Competent Surgery-Anaesthesia Team,Minimizing & Dealing Involved Eventualities, In Well Equipped 'Intensive Care Units',
  With 'Needed Supportive Measures'.
- **Discretion for ?Operative Procedure** Performed, In Appropriation Of Pt's GC & Septicaemia Parametres.
- **Appropriate Antibiotics In Adequate Dosage, Duration** Monitored By Peritoneal Aspirate, Blood C & S , Play **Most Important Role** D/T Changing Strain, Virulence Of Infection & Remote Spread, In Both Categories.

- **Associated Medical Problems** Esp. HIV [74], Malignancy Etc., Previous Surgery, Paediatric Pts,Disease Duration & Previous Treatment Efficacy.

**In Accordance With Available Methods**:[73] **Acute Physiologic And Chronic Health Evaluation II (Apache II) And Mannheim Peritonitis Index (MPI);**

**The Evaluated 'Potential Risk Factors' Include-**

- **General Condition** ; Age (>40 Years)
- **Associated Medical Problems**, Chr. Debilitating Diseases Previous Surgery, Drug Allergy.
- **Disease Duration** & Previous Treatment Efficacy,? Use Of Steroids
- **Type & Virulence Of Infection**, Peritoneal Contamination Dependent Upon Duration, Number, Location And Size Of Perforation,Compounded By Systemic And Metabolic Effects Of Pre-Existing Fever.
- **Septicaemia**:Vitals: High Fever >38.5°C,CVS, Respiratory Status,Urine Out Put: Oliguria, Anuria, Treatment Resistant (↓) U.O
- **Laboratory Indices:-**Hemoglobin Level <8 G/Dl, Elevated ESR,TLC,DLC;Leucocytosis-Absolute,Relative,Leukopenia<3,000WBC/µl. -Renal FunctionTests;Uraemia,Uricaemia,(↑)S.Creatinine Values, Ratios -Liver Function Tests;Hepatosplenomegaly ? Hepato- Biliary Affections, Elevated Transaminase Levels >1.5 Times Normal Values.
- **Available Resources Circumstances:**

**Well Equipped Intensive Care Units;**Proper CVS & Respiratory Monitoring Devices, CVP Line,? SpO2 Levels Needed Ventilatory Support,Haemo/Peritonaeal Dialysis Etc.

**Laboratory Facilities;**Especially For Comparative Monitoring For Serum Electrolytes, Renal Function Tests, Blood Sugar Levels Etc.

**Proper Well Equipped Operation Theatre**; Within Acceptable Asepsis Norms

**Experienced Surgical Team** With Competent Anaesthesia Support,To Minimize OverAll Surgery-Anaesthesia Trauma Stress By Optimal Timings & Dealing Involved Eventualities. Facilities For Other Supportive Therapies

## V.'CONCLUSION'

Amongst **'Commonest Clinical Practice Dilemmas',** Enteric Infections(Salmonellosis) Manifestations,Demand Discrete 'Clinico-Investigatory Assesment',For Implementing The Needed 'Treatment Plan', Aiming Maximal 'Over All Result OutCome',

Of Discussed Vivid Variety Of 'Clinico-Pathological Manifestations', In Variable Resources Circumstances, Especially In Peripheries.

The Listed, **'The Overall Result Outcome Determinants',** Emphasizing

Clinico-Investigatory Variable Indices Of The Disease Process And CoMorbid Conditions, For Deciding **"Management Guidelines Plan",** Practically Acceptable,

In The Available Resources Circumstances, While Achieving 'Maximal ResultOutcomes', Categorized Under,

1. **Medical** (Meticulous Proper ?Appropriate Antibiotics Use, In Adequate Dose Duration, In Accordance With C&S-Peritoneal Aspirate & Or Blood)
2. **Non / Minimal Invasive Radio-Diagnostic Guided Postural Drainages**
3. **Meticulously Performed Judicious Surgical Procedures,** In Conjunction With Other Intensive Supportive Measures,

Hold The **'Keys To Success'** For Typhoid Fever Progression,Perforation Management.

[75]**'OverAll Disease Control Strategies'**,In Consideration Of Global Region Prevalence, Need To Aim Towards, Prevention Of Infection By Safe, Economical Yet Practically Achievable Measures Including Safe Water, Food Safety, Hygeine, Sanitation,Health Education & Vaccination Programmes.

## 'ACKNOWLEDGEMENTS'

With Special Gratitude And Thanks,
For All The 'Study Material Resources' Consulted &
Every Involved Personnel In The Surgical/Anaesthesia, Para-Medical Staff Team Especially Laboratory & Radio-Diagnostics Personnels,
For Constant Co-Operation ThroughOut,
Managing Thousands Of Patients, In Available Resources Circumstances,
SomeTimes In Very Difficult Situations, During Last More Than (2) Decades.

## "REFERENCES"


[1]. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. World HealthOrgan Bull 2004;82:346-53.
[2]. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al. Food-related illness and death in the United States. Emerg Infect Dis 1999;5(5):607–25.
[3]. Giannella Ra. Infectious enteritis and proctocolitis and bacterial food poisoning. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease* . 9th ed. Philadelphia, Pa: Saunders Elsevier; 2010:chap 107.
[4]. Crump NF. Current trends in typhoid fever. Curr Gastroenterol Rep 2003;5:279-86. Miller SI, Peuges DA. *Salmonella* including *Salmonella typh*i. In: Mandel GL, Raphael D. Editors, Principles and practice of infectious diseases. 5th ed., Chruchill Livingstone 2000: 2345.
[5]. Kalra SP et al. Current trends in the management of Typhoid fever. MJAFI 2003; 59:130-5.
[6]. Bhutta ZA, Dewraj HL. Current concepts in the diagnosis and treatment of typhoid fever. BMJ 2006;333:78-82.
[7]. Vallenas C, Hernandez H, Kay B, Black R, Gotuzzo E. Efficacy of bone marrow, blood, stool and duodenal contents cultures for bacteriologic confirmation of typhoid fever in children. *Pediatric Infectious Disease* 1985; 4(5): 496-8.
[8]. Wain J, Diep TS, Ho VA, Walsh AM, Hoa TTN, Parry CM, White NJ. Quantitation of bacteria in blood of typhoid fever patients and relationship between counts and clinical features, transmissibility, and antibiotic resistance. *Journal of Clinical Microbiology* 1998; 36: 1683-7.
[9]. Soewandojo E, Suharto U, Hadi U, Frans P, Prihartini E. Comparative results between bone marrow culture and blood culture in the diagnosis of typhoid fever. *Medical Journal of Indonesia* 1998; 7(S1): 209.
[10]. Kabra SK, Madhulika, Talati A, Soni N, Patel S, Modi RR. Multidrug-resistant typhoid fever. Trop Doct 2000;30:195-7.
[11]. Garcia JA, Damian RF. Typhoid fever. In : Rakel RE,Edward TB, editors. Conn's Current Therapy. 53rd ed. W.B Saunders Co 2001;167-8.
[12]. Schwalbe RS, Hoge CW, Morris JG Jr, O'HanlonPN, Crawford RA, Gilligan PH. In vivo selection for transmissible drug resistance in *Salmonella typhi* during antimicrobial therapy. Antimicrob Agents Chemother 1990;34:161-72.
[13]. Daga MK, Sarin K, Sarkar R. A study of culture positive multidrug resistant enteric fever-changing pattern and emerging resistance to ciprofloxacin. J Assoc Physicians India 1994; 42: 599-600.
[14]. Alam MN, Haq SA, Das KK et al. Efficacy of ciprofloxacin in enteric fever : Comparison of treatment duration in sensitive and multidrug resistant *Salmonell*a. Am J Trop Med Hyg1995;53:306-11.
[15]. Wain J. Quinolone-resistant *Salmonella typhi* in Vietnam: Molecular basis of resistance and clinical responseto treatment. Clin Infect Dis 1997;25:1404-10.
[16]. Soe GB, Overturf GD. Treatment of typhoid fever and other systemic salmonelloses with cefotaxime,ceftriaxone, cefoperazone, and other new cephalosporins. Rev Infect Dis 1987;9:719-36.
[17]. Choo KE, Ariffin WA, Ong KH, Sivakumaran.Aztreonam failure in typhoid fever. Lancet1991;337:498.
[18]. Frenck RW Jr. Azithromycin versus ceftriaxone forthe treatment of uncomplicated typhoid fever in children.Clin Infect Dis 2000;31:1134-8.
[19]. Butler T. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. J Antimicrob Chemother 1999;44(2):243-50.
[20]. Dhanjee A, Sheikh MA, Yaqub M, Alam SE. Orelox (cefodoxime) in typhoid fever. *Journal of the Pakistan Medical Association* 1999; 49: 8-9.
[21]. Leung D, Venkatesan P, Boswell T, Innes JA, Wood MJ. Treatment of typhoid in pregnancy. *Lancet* 1995; 346: 648.
[22]. Cooles P. Adjuvant steroids and relapse of typhoidfever. J Trop Med Hyg 1986; 89:229-31.
[23]. Capoor MR, Nair D, Hasan AS, Aggarwal P, Gupta B. Typhoid fever: Narrowing therapeutic options in India. Southeast Asian J Trop Med Public Health 2006;37:1170-4.
[24]. Tarr PE, Kuppens L, Jones TC, Ivanoff B, AparinPG, Heymann DL. Considerations regarding massvaccination against typhoid fever as an adjunct tosanitation and public health measures :potential use in an epidemic in Tajikistan. Am J Trop Med Hyg 1999;61:163-70.
[25]. Lin FY, Ho VA, Khiem HB, Trach DD, Bay PV, ThanhTC. The Efficacy of a *Salmonella typhi* Vi Conjugate Vaccine in Two-to-Five-Year-Old Children. Engl J Med 2001;344;1263- 9.
[26]. Institute of Medicine. *New vaccine development: establishing priorities. Vol.II. Diseases of importance in developing countries.* Washington DC: National Academy Press; 1986 (Appendix D 14, p. 1-10).
[27]. Mehta SR, Narula HS, Roy SK. Atypical presentationof enteric fever. MJAFI, 1987;43:58-60.
[28]. Everest P, Wain J, Roberts M, Rook G, Dougan G. The Molecular mechanisms of severe typhoid fever. Trends Microbiol 2001;9:316-20.
[29]. Nguyen NC, Everest P, Khoa TT, House D, Murch S, Parry C, *et al*. A clinical, microbiological and pathological study of intestinal perforation associated with typhoid fever. Clin Infect Dis 2004;39:61-7.
[30]. Peiris JS, Thevanesam V, Arseculeratne SN, Kumarakulasinghe CB, Edwards RH. Ileal perforation in typhoid: Bacteriological and immunological findings. Southeast Asian J Trop Med Public Health 1993;24:119-25.
[31]. Mukawi TJ. Histopathological study of typhoid perforation of the small intestines. Southeast Asian J Trop Med Public Health 1978;9:252-5.
[32]. Atamanalp SS, Aydinli B, Ozturk G, Oren D, Basoglu M, Yilirgan MI. Typhoid intestinal perforations: Twenty-six year experience. World J Surg 2007;31:1883-8.3.
[33]. Butler T, Knight J, Nath SK, Speelman P, Roy SK, Azad MA. Typhoid fever complicated by intestinal perforation: A fatal disease requiring surgical management.Rev Infect Dis 1985;7:244-56.
[34]. Nuhu A, Dahwa S Hamza A. Operative management of typhoid intestinal perforation in children.Afr J Paediatr Surg 2010;7:9-13.
[35]. Ekenze SO, Ikefuna AN. Typhoid intestinal perforation under 5 years of age. Ann Trop Paediatr 2008;28:53-8.
[36]. Adeniran JO, Taiwo JO. Typhoid Intestinal Perforation in Children: Salmonella Versus the Surgeon: who is winning the race? Trop J Health Sci 2008;15:61-5.
[37]. Uba AF, Chirdan LB, Ituen AM, Mohammed AM. Typhoid intestinal perforation in children:A continuing scourge in a developing country. Pediatr Surg Int 2007;23:33-9.
[38]. Keenan JP, Hadley GP. The surgical management of typhoid perforation in children. Br J Surg 1984;71:928-9.
[39]. Sitaram V, Moses BV, Fenn AS, Khanduri P. Typhoid ileal perforations: A retrospective study. Ann R Coll Surg Engl 1990;72:347-9.
[40]. Badejo OA, Arigbabu AO. Operative treatment of typhoid perforation with peritoneal irrigation: A comparative study. Gut 1980;21:141-5.

[41]. Golakai VK, Makunike R. Perforation of terminal ileum and appendix in typhoid enteritis: Report of two cases. East Afr Med J 1997;74:796-9.
[42]. Melnik AP. A case of perforation of the duodenum and ileum of typhoid etiology. Sov Med 1966;29:145.
[43]. Saxena V, Basu S, Sharma CL. Perforation of the gall bladder following typhoid fever- induced ileal perforation. Hong Kong Med J 2007;13:475-7.
[44]. Chang YT, Lin JY, Huang YS. Typhoid colonic perforation: A ten year experience. World J Surg 2008;30:342-7.
[45]. Chiu CH, Su LH, He CC, Jaing TH, Luo CC, Lin TY. Perforation of toxic megacolon in non-typhoid Salmonella enterocolitis spares young infants and is immune-mediated. Pediatr Surg Int 2002;18:410-2.
[46]. Wittmann D, Schein M, Codon RE. Management of secondary peritonitis. Ann Surg 1996;224:10-8.
[47]. Malangoni MA. Contributions to the management of intraabdominal infections. Am J Surg 2005;190:255-9.
[48]. Weigelt JA. Empiric treatment options in the management of complicated intraabdominal infections. Cleveland Clin J Med 2007;74:329-37.
[49]. Agarwal S, Gera N. Tuberculosis--an underestimated cause of ileal perforation. J Indian Med Assoc 1996;94:341,352.
[50]. Sharma S, Kotru M, Batra M, Gupta A, Rai P, Sharma R. Limitations in the role of ulcer edge biopsy in establishing the aetiology of nontraumatic small bowel perforation. Trop Doct 2009;39:137-41.
[51]. Akgun Y, Bac B, Boylu S, Aban N, Tacyildiz I. Typhoid enteric perforation. Br J Surg 1995;82:1512-5.
[52]. Pal DK. Evaluation of best surgical procedures in typhoid perforation: An experience of 60 cases. Trop Doct 1998;28:16-8.
[53]. Shah AA, Wani KA, Wazir BS. The ideal treatment of the typhoid enteric perforation-resection anastomosis. Int Surg 1999;84:35-8.
[54]. Shukla VK, Sahoo SP, Chauhan VS, Pandey M, Gautam A. Enteric perforation- single-layer closure. Dig Dis Sci 2004;49:161-4.
[55]. Malangoni M, Inui T. Peritonitis: the Western experience. World J Emerg Surg 2006;1:9.
[56]. Pieracci FM, Barie PS. Management of severe sepsis of abdominal origin. Scand J Surg 2007;96:184-96.
[57]. Koperna T, Shulz F. Relaparotomy for peritonitis: Prognosis and treatment of patients with persisting intraabdominal infections: World J Surg 2000;24:32-7.
[58]. Ahmed HN, Niaz MP, Amin MA, Khan MH, Parhar AB. Typhoid perforation still a common problem: Situation in Pakistan in comparison to other countries of low human development. J Pak Med Assoc 2006;56:230-2.
[59]. Karmacharya B, Sharma VK. Results of typhoid perforation management: Our experience in Bir Hospital, Nepal. Kathmandu Univ Med J (KUMJ) 2006;4:22-4.
[60]. Chatterjee H, Jagdish S, Pai D, Satish N, Jayadev D, Reddy PS. Changing trends in outcome of typhoid ileal perforations over three decades in Pondicherry. Trop Gastroenterol 2001;22:155-8.
[61]. Nguyen VS. Typhus perforation in the tropics: Apropos of 83 cases. J Chir (Paris) 1994;131:90-5.
[62]. Conroy JV. Acute ileitis with ulceration and perforation due to paratyphoid fever; report of eighty-five cases. *Mil Med.* 1957 Feb;120(2):79–92. [PubMed]
[63]. Aziz M, Qadir A, Aziz M. Faizullah: Prognostic factors in typhoid perforation. J Coll Physicians Surg Pak 2005;15:704-7.
[64]. Saxe JM, Cropsey R. Is operative management effective in treatment of perforated typhoid? Am J Surg 2005;189:342-4.
[65]. Paredes C, Cruz J, Diaz-Plasencia J, Prevost M. Prognostic factors in typhoid perforation. Rev Gastroenterol Peru 1993;13:13-9.
[66]. Singh KP, Singh K, Kohli JS. Choice of surgical procedure in typhoid perforation: Experience in 42 cases. J Indian Med Assoc 1991;89:255-6.
[67]. Kurlberg G, Frisk B. Factors reducing mortality in typhoid ileal perforation. Trans R Soc Trop Med Hyg 1991;85:793-5.
[68]. Mock C, Visser L, Denno D, Maier R. Aggressive fluid resuscitation and broad spectrum antibiotics decrease mortality from typhoid ileal perforation. Trop Doct 1995;25:115-7.
[69]. Hosoglu S, Aldemir M, Akalin S, Geyik MF, Tacyildiz IH, Loeb M. Risk factors for enteric perforation in patients with typhoid fever. Am J Epidemiol 2004;160:46-50
[70]. Gedik E, Girgin S, Taçyildiz IH, Akgün Y. Risk factors affecting morbidity in typhoid enteric perforation. *Langenbecks Arch Surg* 2008; 393: 973-977
[71]. Edino ST, Yakubu AA, Mohammed AZ, Abubakar IS. Prognostic factors in typhoid ileal perforation: A prospective study of 53 cases. J Natl Med Assoc 2007;99:1042-5.
[72]. Mohil RS, Singh T, Arya S, Bhatnagar D. Risk adjustment is crucial in comparing outcomes of various surgical modalities in patients with ileal perforation. Patient Saf Surg 2008;2:31. .
[73]. Adesunkanmi AR, Oseni SA, Adejuyigbe O, Agbakwuru EA. Acute generalized peritonitis in African children: Assessment of severity of illness using modified APACHE II score. ANZ J Surg 2003;73:275-9.
[74]. Gotuzzo E, Frisancho O, Sanchez J, Liendo G, Carillo C, Black RE, Morris JG. Association between the acquired immunodeficiency syndrome and infection with *Salmonella typhi* or *Salmonella paratyphi* in an endemic typhoid area. *Archives of Internal Medicine* 1991; 151: 381-2.
[75]. Crump J, Yousef FG, Luby SP,Wasfy MO,Rangel JM,Talaat M Et Al. Estimating The Incidence Of Typhoid Fever & Other Febrile Illnesses In Developing Countries Emerging Infectious Diseases 2003,9:539-44.