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PREVALENCE OF MYCOBACTERIUM OTHER THAN TUBERCULOSIS IN THE PHILIPPINES

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Setting: A developing country with a high prevalence of tuberculosis infection.
Objective: To determine the prevalence of Mycobacterium other Than Tuberculosis (MOTT) in the Philippines.
Method: Sputum specimens were obtained from patients with abnormal chest radiography in a representaive sample nationwide and smears and culture for acid fast bacilli were done. Niacin-negative mycobacterial isolates were considered as MOTT.
Results: The prevalence of MOTT was 31.9 per thousand nationwide. It was higher in males than females, it was highest at more than 50 age group and it was higher in urban compared to rural population.
Conclusion: The prevalence of MOTT in the Philippines, a tropical country with a high prevalence of tuberculosis is high. This may affect the results of PPD skin test.

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COMPARATIVE EVALUATION OF VARIOUS DIAGNOSIS MODALITIES**

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Neuro-tuberculosis (NTB) constitute 5% of all extrapulmonary cases of tuberculosis. Tubercular meningitis is the most common form followed by tuberculoma and spinal cord tuberculosis. Clinical presentation is affected by immune status and in tuberculoma signs and symptoms may be absent. Direct demonstration in smear and culture in NTB consumes time and need early diagnosis. We report a restrospective hospital based study to see the utility of various diagnostic modalities like A60 ELISA in smear and culture negative cases and with that of pulmonary and other extrapulmonary cases during Jan 94-Dec 99. A total of 30 NTB cases were compared by clinical MRI and treatment outcome. A total of 781 specimens (590 serum, 184 CSF) collected from patients and control subjects were devided into group1: NTB (393 sera and 167 CSF), group 2: Extrapulmonary (94), group 3: Normal Control (80), group 4: Clinical radiological and microbiological positive control (30), group 5: disease control (17). Estimation in CSF showed in group 1: IgM positivity were lower than sera but IgG positivity was similar as in sera. The antibody positivity was better in TBM than in other subgroups of NTB. IgA antibody was positive in 56%, 61%, 81% in pulmonary TB, NTB and extrapulmonary cases. The positive antibody level correlated with MRI findings. Thus the serological study will be an adjunct for rapid diagnosis of NTB and can be picked up by applying these two tests simultaneously.

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VACCINES FOR ENTERIC BACTERIAL PATHOGENS: STATE OF THE ART

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Towards the end of the century, acute diarrhea remains a major cause of morbility and mortality in children, especially in the developing country. Increasing knowledge on epidemiology and pathogenic mechanisms of diarrheogenic bacteria has guided vaccine strategies currently under development. The most promising initiatives are focused on two widely prevalent pathogens. *Shegiella* and *Enterotoxigenic E. coli* (ETEC).

Three strategies have been targeted for *Shegiella*. 1) Genetically modified live attenuated prototype strains with deletions of specific virulence genes and/ or mutations of virulence associated-metabolic pathway genes are in initial phases of evaluations. 2) Recombinant vaccines based on use of carrier bacteria will be incorporated relevant *Shegiella* antigens genes are also being evaluated.

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Examples are *S. typhi* Ty21 a carrier expressing *Shigiella LPS and E coli K/2* expressing virulence genes of *Shegiella flexneri 2 a*, 3) Submit inactivated vaccines including purified, detoxified LPS from *S dysenteriae I, S flexneri2 a*,and *S sonnei* conjugated to proteins carriers have been developed and seen promising. The late was 7% protective in a population of Israeli soldiers.

ETEC, an important cause of acute diarrhea in child and travels diarrhea in adults has different virulence factors, e.g. an adherence fimbria denominated colonization factors (CFA), and two potent enterotoxins ST and ET. Vaccines strategies have focused mainly on eliciting immune responses against these virulence factors. ET/ST avoid and purified CFA have been tested in oral formulations with poor immunogenic responses. The latter have been incorporated into biodegradable spheres in order to surpass that acid gastric barrier and to facilitate sustained release. strategy that has so far, not significantly improved immunologenecity. New adjuncts are being tested. Following the cholera model, an recombinant ETEC that expresses CFA, conjugated with subunit B of cholera toxin proved to be safe but poorly immunogenic in phase II trials. Recombinant vaccines using a carrier bacteria is also being evaluated: *S flexneri* carrier that expresses CFA could eventually protect against both *Shegiella* and *ETEC* infections.

A completely new and potentially revolutionary approach is the developement of transgenic plants that have incorporated bacterial virulence genes. in this case, subunit B of the ET toxin, nad are capable of expressing the protein. Transgenic potatoes, TH110-ST synthesize subunit B antigens that when ingested raw, elicit a local systemic immune response similar to that observed for natural infections. This strategy is of low cost and is concievable for other potential vehicle candidates such as bananas and other fruits and/or vegetables that are traditionally eaten raw.

Development of new vaccines offers many challenges to creative scientists capable of combining knowledge on bacterial-host interaction and technology. The recent developments should have a significant impact in prevention of diarrheal diseases in the intermediate future.

INSTRUCTIVE CASE-DENOUEMENT

Pustular Lesions and Poor Sensorium in a 9 year old boy

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This is a case of a 9-year old boy with a 3-day history of fever. a transient generalized rash and with decrease in sensorium few hours prior to admission. He was referred to the service consultant. and was assesssed to have Toxic Shock Syndrome because of the following shock (hypotension) with a history of puncture wound. acute fever. erythematous rash. gastrointestinal symtoms. liver and central nervous system abnormalities. Ceftriaxone was discontinued and oxacillin was retained and amikacin was started at 15 mg/kg/day. Immunoglobulin Intravenous was suggested to be given. Unfortunately, while the patient was on IVIg transfusion he went into cardiac arrest and attempts at resuscitation were made. The patient's relatives then requested to discontinue resuscitation which was then 22nd hospital hour. Blood culture taken on admission later grew *Staphylococcus aureus* sensitive to Oxacillin.

The most striking aspect of TSS is the rapidity with which the manifestations can present and progress in a previously healthy individual of any age or sex . Thus early recognition and agressive management is of utmost importance.

The diagnosis of Staphylococcal Toxic Shock Syndrome is based on Clinical case definition':

- Fever: temperature = 38.9 ℃
- Rash: diffuse macular erythroderma
- Desquamation: 1-2 week after onset, particularly palms and soles
- Hypotension: systolic blood preasure 90 mmHg for adults. lower by 5th percentile by age for children younger than 16 y.o. orthostatic drop of diastolic blood preasure of 15 mmHg from lying to sitting; orthostatic syncope or orthostatic dizziness
- Multisystem involvement: 3 or more of the following:
  1. Gastrointestinal: vomiting or diarrhea at onset of illness
  2. Muscular: severe myalgia or creatinine phosphokinase level greater than twice the upper limit of normal

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3. Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
4. Renal: BUN or serum creatinine level greater than twice the upper limit of normal or urinary sediment with 5 WBC/HPF in the absence of UTI
5. Hepatic: total bilirubin, AST, or ALT level greater than twice the upper limit of normal
6. Hematologic: platelet count of <100,000x10⁹/L (<100 10^3/ul)
7. Central nervous system: disorientation or alterations in conciousness without focal neurologic sign when fever and hypotension are absent

Negative results on the following test, if obtained: Blood, throat, or cerebrospinal fluid cultures: blood culture may be positive for *Staphylococcus aureus* Serologic test for Rocky mountain spotted fever, leptospirosis, or measles.

Case classification

Probable: a case with 5 or 6 of the aforementioned clinical findings

Confirmed: a case with 6 of the clinical findings, including desquamation.

If the patient dies before desquamation could have occured, the other 5 criteria constitute a definitive case.

The patient presented is a confirmed case of Toxic Shock Syndrome fulfilling 6 of the clinical findings and blood culture confirmed the presence of *S. aureus*. *Streptococcus pyogenes* causing toxic shock syndrome also ocurs and there are some differences in clinical manifestations as well as case definitions (which will not be discussed in this article)

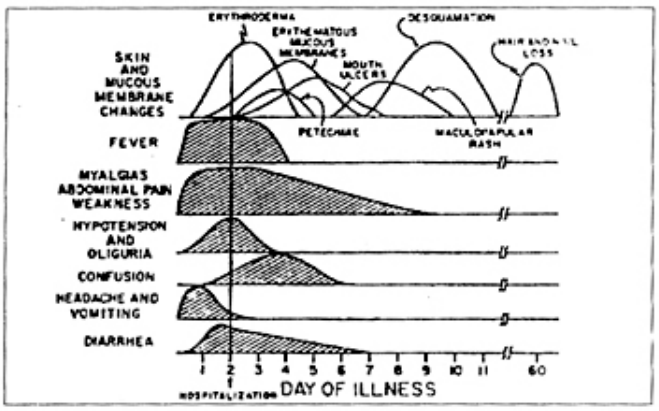

Figure 1. Composite drawing of major systemic skin and mucous membrane manifestation of toxic shock syndrome[3].

Todd and Fishaut described in 1978 seven children aged 8-17 years with the clinical features as describe above[4].The entity was named Toxic shock syndrome and was later considered to be synonymous with staphylococcal scarlet fever,a disease entity recognized since 1927. In 1980, the TSS cases were strongly associated with tampon use of menstruating adolescent and young women with a marked increase in incidence (90% of cases). Menstrual TSS reached epidemic proportions in 1980-81 and was attributed to the introduction of a hyperabsorbable tampons in the market[5]. With the withdrawal from the market of this product the cases of menstrual TSS has decreased and non-menstrual TSS have become epidemiologically important. TSS also occured in children, men and, non-menstruating women which are asssociated with wound infection, nasal packing, sinusitis, tracheitis, empyema, abscesses, burns, osteomyelitis, and primary bacteremia. Non-menstrual cases of TSS accounted for <10% in 1979-1980 and 50% in 1996[6]. The Centers for Disease Control and Prevention in 1996 reported in incidence of 0.6 cases per 100,000 people making TSS a relatively rare condition.

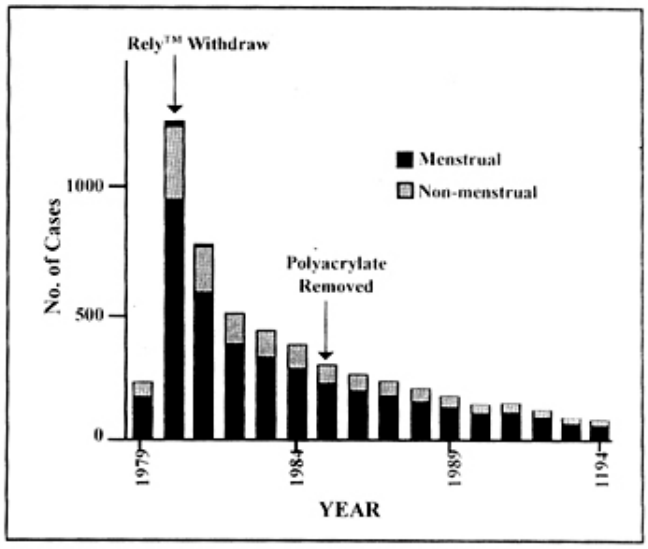

Figure 2. Menstrual and non-menstrual cases of toxic shock syndrome reported to the Centers for Disease Control and Prevention. Indicated are the withdrawal of the Rely brand tampons and the supeabsorbent tampons containing polyacrylate rayon[6].

Locally in the Department of Pediatrics at UP-PGH in a 6year review from 1994-2000, non-menstrual TSS cuased by *S aureus* revealed 2 cases in 1994 and 1995 both are female ages 4 moths and 6 years old. In 1998, there was a case of an 18 year old male. No

mortalities were reported. Unfortunately, in the Philippines, it is probable that many cases are unrecognized and misdiagnosed, thus the true incidence of the disease is not known.

Table 1. Risk Factor for Nonmenstrual Staphylococcal Toxic Shock Syndrome[7]

I. Colonization with or introduction of toxic producing *Staphylococcus aureus*

II. Absence of protective antitoxin antibody

III. Infected site

- Primary *S aureus* infection (carbuncle, cellulitis, dental abscess, empyema, endocarditis, folloculitis, peritonitis, abscess, pneumonia, pyarthrosis, pyomyositis, sinusitis,tracheitis)
- Postoperative wound infection (abdominal, breast, ear, nose, and throath, genitourinary, cesarean section,dermatologic, neurosurgical, orthopedic)
- Skin or mucous membrane disruption (burns, dermatitis, postpartum, superficial or penetrating trauma, viral infection, infuenza, pharyngitis, varicella)
- Surgical or nonsurgical foreign body placement (augmentation mammoplasty, catheters, diaphram, sponge, surgical prostheses, stents, packing material or sutures,)
- No obvious focus of infection (vaginal or pharyngeal colonization)

Staphylocccus aureus mediated TSS usually is caused by strains producing toxic shock syndrome toxic-1 (TSST.1). Most of this strains also produce at least one of the *staphylococcu enterotoxins*. Some TSS-1 negative strains of *S aureus* has been implicated with non-menstrual cases of TSS.

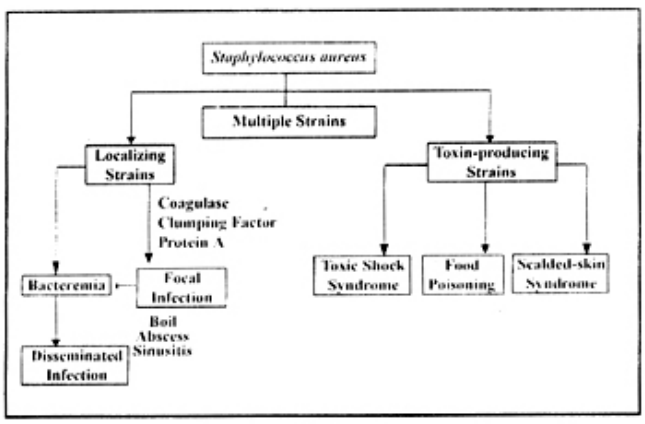

Figure 3. Relationship of virulence factors to diseases with Staphylococcus aureus[8].

Like endotoxin mediate shock, TSS is considered a capillary leak syndrome manifested as hypotension, hypoalbuminemia and generalized non-pitting edema.

There are three mechanism by which the *Staphylococcus aureus* Toxic Shock Syndrome Toxin-1 causes hypotension: (1) TSS-1 induced cytokine release- thru the activation of T cells (2) TSS-2 induce hypersensitivity to endotoxin (3) Direct effects of TSS-1 on endothelial cells causing the release of vasoactive mediators such as TNF-α from host leukocytes that may cause hypotension.

The management of TSS is outlined below. The first priority in the management is resuscitation of the patient which includes rapid fluid replacement as well as the management of respiratory or cardiac failure. Combination antibiotic therapy is advocated giving a β-lactam anti staphylococcus agent such as oxacillin, with a protein synthesis inhibitor such as clindamycin or an aminoglycoside. This is necessary to eradicate organisms and to prevent recurrences[9]. This regimen must be continued for 10-14 days. IVIG has been found to decreased mortality in rabbit models of TSS[10]. Due to lack of randomized control trials in humans and its high cost, IVIg has been reserved for cases who continue to deteriorate in spite several hours of fluid resuscitation.

Table 2. Management of Staphylococcal Toxic Shock Syndrome[5]

- Fluid management to maintain adequate venous return and cardiac filling preasures to prevent end-organ damage
- Parenteral antimicrobial therapy at maximal dose for age for Anticipatory management of multisystem organ failure
- Kill organism with bactericidal cell wall inhibitor (B-lactamse-resistant antistaphylococcus antimicrobials)
- Stop enzyme, toxin or cytokine production with protien synthesis inhibitor (clindamycin)
- Immune Globulin Intravenous may be considered for infection refractory to several hours of aggressive therapy, presence of undrainable focus, or persistent oliguria with pulmonary edema

The mortality rate for non-menstrual TSS is 4.3-17.1%[11]. The majority of cases will have full recovery with intense scaling and desquamation 1-2 weeks after onset of the illness. Recurrences may occur if initial

disease was inadequately treated. Sequelae which were noted in a minority of those who recovered include prolonged fatigue, loss of nails and neuropsychologic abnormalities. Since the prognosis is excellent for most cases, early recognition is of paramount importance to institute aggressive management of multi-organ dysfunction and combination antibiotic therapy in order to decrease morbidity and mortality.

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