AAFP GLOBAL HEALTH SUMMIT

Primary Health Care and Family Medicine: Health Equity for All

How Practical Research Can Improve Clinical Care in the Developing World

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Objectives

- Examine the potential benefits of practical clinical research in a health care setting in the developing world.
- Review studies of acute undifferentiated febrile illness and acute diarrhea in the Ecuadorian Amazon basin as models of impactful research.
- Consider how family physicians can become involved in practical research in resource-limited settings overseas.

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Some generalizations about health care facilities in the developing world

- Limited resources:
  - staff
  - finances
  - diagnostic capabilities
  - therapeutic options
- High demand:
  - number of patients
  - severity of illness

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Why add research?

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- Added revenue to increase staff and/or services
- Disseminated results extend impact

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- No need to write grants
- Good partners: U.S. Navy or U.S. Army
  National or foreign universities
  Other established researchers (American Society of Tropical Medicine and Hygiene)

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Diagnostic Capabilities at Hospital Vozandes del Oriente

- CBC
- Basic chemistry (BMP, LFTs)
- Serology: RPR, HBSAg, HIV
- Thick and thin blood smears for malaria
- ESR
- Urinalysis
- Stool exams
- CSF analysis
- Microbiology: Gram stains, AFBs, routine bacterial and TB cultures
- Plain x-rays
- Ultrasound
- Upper and lower endoscopy

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- Knowledge of local epidemiology may be very limited

Methods

- 533 patients with fever ≤ 7 days (≥ 38.0 C)
- Excluded patients with readily identifiable focus of infection
- Demographic and clinical data
- CBC and thick blood smear for malaria
- Rapid diagnostic tests (dengue, leptospirosis)
- *Acute and convalescent* serum samples sent for indirect fluorescent antibody tests (IFA), viral culture, serology and PCR
- Limitations: Battery of tests was not exhaustive (e.g., typhoid not included)

Acute Undifferentiated Febrile Illness Study

Partners: Hospital Vozandes del Oriente
Shell, Ecuador

Hospital de la IV División de Amazonas
Puyo, Ecuador

U.S. Navy Medical Research Institute Detachment
Lima, Peru

Short-term benefits

- Funds for additional staff

Purpose

- Identify pathogens that cause acute undifferentiated febrile illnesses in the Ecuadorian Amazon basin.
- Determine clinical characteristics that might be useful in differentiating between the various etiologic agents.
- Develop a protocol for diagnosis and treatment.
- Share findings with the Ministry of Health and other health care professionals in the region and elsewhere.

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Results

- 304 of 533 patients returned for follow-up
- Pathogens identified in 40% of patients
  - Leptospirosis – 13.2%
  - Malaria – 12.5%
  - *Rickettsia* spp.– 5.9%
  - Dengue – 5.3%
  - Q Fever (*Coxiella*)– 4.9%
  - Brucellosis, Ilheus, Venezuelan Equine Encephalitis, Oropouche, St. Louis Encephalitis – < 2%
- All except malaria were previously unrecognized in the area.
- Distinguishing clinical features: rash was more common in dengue (25% vs 3.5%, p<0.001)

Short-term benefits

- Funds for additional staff
- Rapid diagnostic tests and all other lab supplies
- -70 degree C. freezer
- Free labs and follow-up visits for participants

How to distinguish between potential pathogens

- Extremely difficult in most clinical settings and early in course

Short-term benefits

- Funds for additional staff
- Rapid diagnostic tests and all other lab supplies
- -70 degree C. freezer
- Free labs and follow-up visits for participants
- Access to consultants

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  Dengue: tourniquet test

Leptospirosis

- Conjunctival suffusion in 55% of patients
- Unique to leptospirosis - not a conjunctivitis

Lin CY, Chiu NC, Lee CM. Leptospirosis after typhoon. Am J Trop Med Hyg 2012; 86:187

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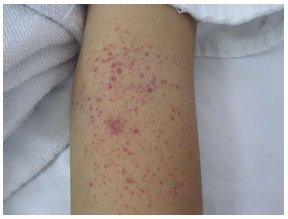
Dengue: tourniquet test



Siripen Kalayanarooj in "Dengue virus infection: Clinical manifestations and diagnosis" UpToDate

1. Inflate BP cuff on arm to midway between systolic and diastolic BP. Maintain for five minutes.
2. Examine skin distal to the BP cuff for petechiae at least one minute after pressure is released.
3. 10 or more petechiae in a one square inch area is considered positive.
4. 58% sensitivity, 71-89% specificity, 70% negative predictive value

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- Need for prompt treatment: Leptospirosis, Q fever, Rocky Mountain Spotted Fever
- Desperate need for accessible tests that are sensitive and specific for early diagnosis

Summary of Treatment of Identified Pathogens

– Leptospirosis	**doxycycline** or azithromycin (mild), IV penicillin G or ceftriaxone or cefotaxime (severe)
– Malaria	ACT (*falciparum*) or chloroquine/ primaquine (*vivax*)
– *Rickettsia* spp.	**doxycycline** (chloramphenicol)
– Dengue	acetaminophen (**avoid NSAIDs**)
– Q Fever (*Coxiella*)	**doxycycline** or **ciprofloxacin** (erythromycin /azithromycin/TMP-SMX)
– Brucellosis	**doxycycline** + **ciprofloxacin**
– Misc. viruses	acetaminophen/supportive care

Protocol for AUFI at Hospital Vozandes del Oriente

- Rule out malaria
- Treat adults empirically with doxycycline (leptospirosis, Q fever, *Rickettsia* spp.) -- erythromycin for children, pregnant or breastfeeding women
- Consider typhoid – ciprofloxacin or 3rd generation cephalosporin
- Acetaminophen prn (avoid NSAIDs)

Discussion:

Acute Undifferentiated Febrile Illness Study

Impact of research

- All identified pathogens were previously unrecognized, other than malaria
- Diagnostic difficulty: Limits of rapid serologic tests (e.g. dengue: 6-7 days, leptospirosis: 7-10 days)
- Substantial, lasting change in approach to empiric treatment of undifferentiated febrile illnesses
- Results shared with Ministry of Health: dengue control campaign
- Published results in *American Journal of Tropical Medicine & Hygiene* (>70 citations to date)

Diarrheal Illness in the Developing World

- 1.5 to 2 million deaths worldwide annually

JAMA – Jan. 25, 2013; WHO - 2015

Potential Pitfall:

Policy of empiric antibiotic therapy for AUFI may inadvertently promote antibiotic resistance.

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- Fifth leading cause of death in children under 5 years of age

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- Leading cause of death in older children

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Definition of Acute Diarrhea

- At least 3 loose or watery stools per day
- Duration of < 14 days

Diarrheal Illness in the Developing World

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- Leading cause of death in older children
- Second leading cause of death – all ages

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Standard of Care in Ecuador (early 2000's)

- Oral or IV hydration

Diarrheal Illness in the Developing World

- 1.5 to 2 million deaths worldwide annually
- Fifth leading cause of death in children under 5 years of age
- Leading cause of death in older children
- Second leading cause of death – all ages
- Extremely common due to poor sanitation

JAMA – Jan. 25, 2013; WHO - 2015

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- Oral or IV hydration
- Oral trimethoprim-sulfamethoxazole

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- High proportion of PMN's on stool exam = bacterial etiology

Bacterial Enteric Pathogen Study

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Standard of Care in Ecuador (early 2000's)

- Oral or IV hydration
- Oral trimethoprim-sulfamethoxazole
- High proportion of PMN's on stool exam = bacterial etiology
- Stool cultures not generally available

Bacterial Enteric Pathogen Study: Purposes

- Identify the bacterial pathogens that cause acute diarrhea in the Amazon basin of Ecuador.

Very few studies on the etiology of acute diarrhea in Latin America – and fewer still on antibiotic resistance of bacterial pathogens

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Bacterial Enteric Pathogen Study: Purposes

- Identify the bacterial pathogens that cause acute diarrhea in the Amazon basin of Ecuador.
- Determine the antibiotic resistance of these pathogens.
- Identify symptoms and clinical findings that can differentiate between viral and bacterial etiology.

Results

145 pathogens were isolated from the 124 positive stool cultures.

Methods

- Clinical data and stool samples from 410 patients with acute diarrhea (60% less than 6 years of age)
- Microscopic exams, bacterial cultures and *Campylobacter* antigen tests performed

Bacterial Enteric Pathogens Isolated

Shigella	15.6%
Enterotoxic E. coli	13.2%
Salmonella	2.2%
Campylobacter	2.0%
Citrobacter	1.5%
Plesiomona	0.5%
Aeromona	0.5%

Results

Bacterial enteric pathogens were isolated from 30.2% (124/410) of patients with acute diarrhea.

Overall Antibiotic Sensitivity

Ciprofloxacin	97.1%
Ceftriaxone	96.5%
Gentamicin	92.9%
Nalidixic Acid	88.7%
Azithromycin	73.0%
Cephalothin	65.2%
Chloramphenicol	61.0%
Amoxicillin/Clav. Acid	56.7%
Ampicillin	38.3%
Trimethoprim-Sulfa	37.8%
Tetracycline	27.7%
Erythromycin	14.9%

Clinical Factors Associated with Bacterial Enteric Pathogens

- No statistical association between bacterial etiology and age, sex, daily number of stools, nor mucus in stools
- Association ($p<0.05$) between history of visible blood in stool or fever and having a positive bacterial stool culture

When to Use Antibiotics

- Hard to be certain of bacterial etiology
- The probability of a bacterial infection increases when there is visible blood in the stool or fever – but the absence of these signs doesn't rule out a bacterial cause.

Positive Predictive Value and Negative Predictive Value of Stool PMN's

Stool PMN's	PPV	NPV
26-50%	39%	73%
51-75%	38%	73%
76-100%	45%	77%

When to Use Antibiotics

- Hard to be certain of bacterial etiology
- The probability of a bacterial infection increases when there is visible blood in the stool or fever – but the absence of these signs doesn't rule out a bacterial cause.
- The absence of stool PMN's reduces the probability of a bacterial infection – but doesn't rule it out.

When to Use Antibiotics

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Effective Antibiotic Treatment in the Ecuadorian Amazon Basin

Adults (not pregnant nor lactating):

- Ciprofloxacin PO or IV
- Gentamicin IV or IM
- Ceftriaxone IV or IM

Children and Pregnant/Lactating Women:

- Gentamicin IV or IM
- Ceftriaxone IV or IM
- Second or third generation oral cephalosporins

Use of Fluoroquinolones in Children

- "Second line antibiotics in children in rare situations …gastroenteritis due to Salmonella and Shigella"

American Academy of Pediatrics - 2000 Redbook

- Systemic fluoroquinolones if no safe and effective alternative exists, or if oral fluoroquinolone therapy is a reasonable alternative to IV therapy with a different class of antibiotics

AAP Committee on Infectious Diseases, 2016

Antibiotic Therapy for Acute Diarrhea?

- If bacterial etiology, antibiotic therapy decreases the duration of illness, fever, cramping and transmission.

(Tong et al., JAMA 1970; Bennish et al., J Infect Dis 1990; Christopher et al, Cochran Database Syst Rev. 2010)

Duration of Treatment

Only 1 - 5 days are needed

(Theilman y Guerrant, NEJM 2004)

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- Trend toward limiting antibiotic use (antibiotic stewardship): "Selective use of antibiotics." (WHO 2004)

Bacterial Enteric Pathogen Study: Impact

- Use of oral trimethoprim-sulfamethoxazole was discontinued
- Use of stool exam for PMN's was discontinued
- Recognized that 30% of acute diarrhea cases were bacterial
- Effective antibiotics used judiciously for suspected bacterial enteritis

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- Trend toward limiting antibiotic use (antibiotic stewardship): "Selective use of antibiotics." (WHO 2004)
- Antibiotics (fluoroquinolones, azithromycin X 1-3 days) recommended for moderate to severe traveler's diarrhea (double standard?) (Riddle et al., J Travel Med. 2017)

Discussion:

Bacterial Enteric Pathogen Study

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Takeaway thoughts

- Practical clinical research can be helpful in improving the quality of health care in a developing world setting.
- Consider how you could make a lasting impact through:
  1. Identifying clinical questions that need answers
  2. Developing a research project
  3. Partner with other colleagues in conducting research