A COST EFFECTIVE AND EFFECTIVE APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF ACUTE INFECTIOUS DIARRHEA*

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WHAT is best for an individual patient must remain the physician's central goal, but increasing cost consciousness raises difficult questions about some of our traditional practices. It forces a glaring light on how resources are allocated in a finite world. We in the health profession are forced to examine the benefit of a test, procedure, or treatment regimen in light of its monetary as well as its human costs. Critical appraisal of the appropriateness of some of our approaches may reveal ways to improve our effectiveness as well as our efficiency, especially with the development of new tools for understanding and diagnosis of disease etiologies. This is particularly true of our approach to the diagnosis and management of the common problem of acute infectious diarrhea. During the last two decades there have been numerous advances in the recognition of "new" bacterial, viral, and parasitic enteric pathogens. A growing range of diagnostic tools, treatments, and vaccines are rapidly being brought into practical use by advances in molecular biology and immunology. These advances necessitate critical reappraisal of our traditional approach to indiscriminate stool culture for *Salmonella* and *Shigella* for acute infectious diarrheas. Our goal therefore is a better informed use of the history, physical findings, and available labora-

*Presented as part of the Fourth Annual SK & F/FSK Anti-Infective Conference, *Controversies in Diagnosis and Management of Infectious Disease*, held by the Division of Infectious Diseases/Epidemiology of the College of Physicians and Surgeons of Columbia University and funded by a grant from Smith-Kline French Laboratories/Fujisawasa-Smith-Kline at Orlando, Florida, September 7-9, 1986.

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tory tools realistically to diagnose and appropriately manage the very common patients with uncomplicated noninflammatory diarrhea, less common patients with inflammatory enteritis, and the relatively infrequent patients from special settings in need of more specific diagnosis and treatment.

Is Stool Culture One of the Most Cost Ineffective Laboratory Tests We Do?

The excessive cost of inappropriate clinical and laboratory tests is increasingly recognized. This is especially applicable to routine stool cultures. Examined on a cost-per-positive basis, these may run as high as a staggering $900-$1,200 (Table I). As with many laboratory and other diagnostic tests, ineffectiveness is due to two factors: the use of tests sensitive only for relatively infrequent causes of an illness and that therefore do not identify the much more common causes and poor selection of cases with a greater likelihood of a cause for which the test is designed. Tremendous advances during the last two decades have been made in the recognition of a wide variety of bacterial, viral, and parasitic enteric pathogens in both normal and immunocompromised patients. Far more common than *Salmonella* and *Shigella* combined are *Campylobacter jejuni* infections that cause a similar inflammatory diarrhea. More common than all of these in the United States are rotaviral infections and abroad, in tropical developing areas, are enterotoxigenic *E. coli.* In special situations, cytotoxigenic *Clostridium difficile, Cryptosporidium, Yersinia enterocolitica, Vibrio* and other enteric pathogens should be considered. Consequently, the indiscriminate unselective use of stool cultures for *Salmonella* and *Shigella* will yield positive results in only 1.5-2.5% of cases with the resultant huge cost for each positive result as shown in Table I.

The second problem, inappropriate selection of cases for specific laboratory tests, also contributes to their ineffectiveness. Depending on age, exposure, and susceptibility, each American has 1.8-2.1 acute gastrointestinal illnesses each year.[1,2] Indeed, data from several laboratories all strongly suggest that a readily definable subset of illnesses can indeed be identified with a much greater likelihood of yielding a positive culture for *Salmonella, Shigella,* or *Campylobacter jejuni.*[3-6]

As previously reported and as shown in Table I, the routine addition of *Campylobacter jejuni* whenever there was an indication for *Salmonella* and *Shigella* culture greatly increased the yield of positive culture results. These

TABLE I. PERCENT YIELDS AND COSTS OF STOOL CULTURES

(n)	*Salmonella or Shigella*	*C. jejuni*	*Yersinia*	*Total*	*Cost per positive result*
Massachusetts General Hospital 1979 (2,468)	2.4	—	—	2.4	$ 952
University of Virginia Hospital 1979-81 (2,020)	1.5	—	—	1.5	$1200
University of Virginia Hospital 1981-82 (1,558)	4.0	4.6	0.1	8.7	$ 264
Pediatric outpatient 82, 1984-86 (305)	11.5	6.6	0.7	18.7	$ 118
Cup specimens with fecal polymorphonuclear leukocyte exam	30	46.7	—	76.7	$ 30

Adapted from references 3, 5, 6.

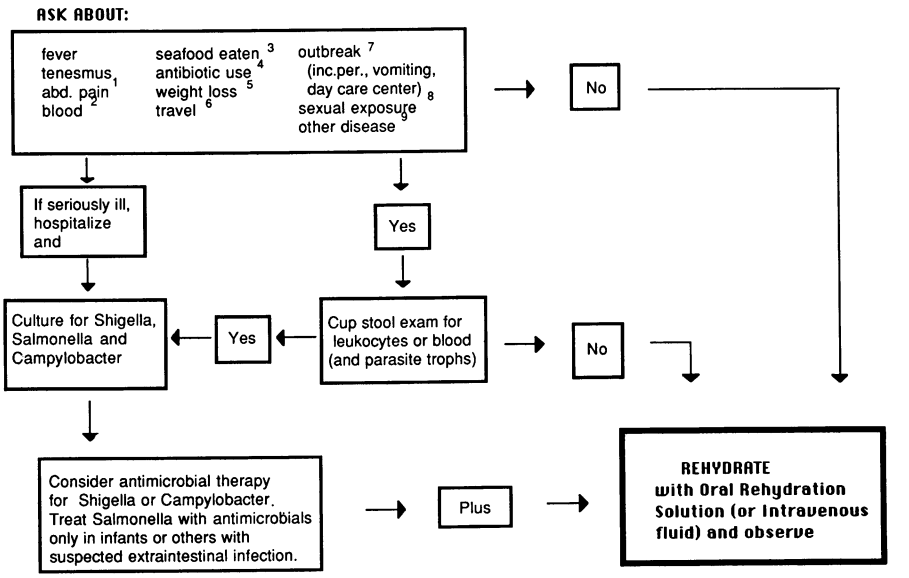
findings are consistent with those of Blaser et al. and others who consistently find that *C. jejuni* is often found in numbers that exceed *Salmonella* and *Shigella* infections combined.[4-6] Shown in Table I is evidence for an increased yield for *Salmonella* and *Shigella,* related to an educational approach regarding the improved selection of patients with a greater likelihood of an inflammatory diarrhea.

An Approach to Diagnosis and Management: A Simple Algorithm

In dealing with patients with the extremely common problem of acute infectious diarrhea (1.8-2.1 illnesses/person/year, depending on age, exposure, and susceptibility), it is both pathogenically and practically useful to consider whether the patient has noninflammatory or inflammatory diarrhea. Noninflammatory diarrhea is much more common, and usually arises in the upper small bowel by a mechanism that involves enterotoxin or some other alteration of small bowel absorptive physiology to cause watery, noninflammatory diarrhea. Although cholera is the classic example, similar illnesses may be caused by enterotoxin producing *E. coli* throughout tropical developing areas as well as by rotaviruses (particularly in small children), Norwalk-like viruses, several types of food poisoning, and even parasitic infections such as giardiasis. Typically, these illnesses primarily involve watery diarrhea, with or without nausea and vomiting, minimal or lowgrade fever, and tend to be self-limited, requiring primarily rehydration. In contrast, inflammatory diarrhea usually arises by mucosal invasion, typically in the colon or distal small bowel to cause inflammatory, often bloody dysentery, characterized by tenesmus (frequent, painful defecation, sometimes with only small

volumes of mucus, pus, and blood) and often a high fever. Classic causes of dysentery include shigellosis and amebiasis, as well as invasive *E. coli, Salmonella* enteritis, and now *Campylobacter jejuni* and cytotoxin producing *Clostridium difficile* in most areas. Invasive diarrhea can often be suspected from a characteristic history of fever, tenesmus, abdominal pain, and even bloody diarrhea. This suspicion can usually be confirmed by examination of a cup fecal specimen for neutrophils and blood. As suggested in the algorithm in the figure, this presentation with fecal leukocytes or serious illness with fever, tenesmus, severe abdominal pain, or bloody diarrhea should prompt fecal culture for *Shigella, Salmonella,* and *Campylobacter jejuni.* If shigellosis can be suspected (as in an outbreak in which it has already been documented), prompt, effective antimicrobial therapy with an agent such as sulfamethoxazole-trimethoprim (if the organism is susceptible) can be expected to reduce the duration and severity of the systemic and diarrheal illness as well as fecal shedding of the organism. In contrast, uncomplicated *Salmonella* gastroenteritis will only have prolonged fecal shedding of the organism, with a potentially greater chance of clinical relapse if currently available antimicrobials are given. The efficacy of erythromycin for documented *Campylobacter jejuni* infections, even when given early, remains debated. In contrast to *Salmonella* infection, erythromycin treatment of *C. jejuni* infections will promptly eradicate susceptible *C. jejuni* from the stool, and might reduce a 10 to 30% relapse rate. However, even early treatment fails to have an appreciable impact on the duration or severity of enteric or systemic symptoms of *C. jejuni* enteritis.[7] Adequate rehydration and maintenance fluid and electrolyte therapy is imperative in any type of diarrheal illness. This can usually be readily and optimally accomplished with a glucose-electrolyte containing oral rehydration solution and by adequate observation and followup.

Common situations suggesting likely etiologies. Important in the diagnostic approach to any patient is recognition that every individual presents with a very specific setting and history that must be taken into account. For acute infectious diarrhea, this includes age, season, clinical presentation, and a history of specific exposures as noted in the algorithm in the figure. In the United States, the highest attack rates of diarrheal illnesses occur during the winter months, and the population at greatest risk are young children. Winter diarrhea is usually noninflammatory and most often due to viral agents. Young children with noninflammatory, winter diarrhea (particularly those less than two years of age) have rotavirus as the leading recognized etiologic agent in approximately 8% of cases in community based studies[2] and



Approach to diagnosis and management of acute infectious diarrhea. Reproduced by permission from Guerrant, R.L.: Campyobacter Infections. In: *Cecil Textbook of Medicine*, Wyngaarden, J.B., and Smith, L.H., Jr., editors. Philadelphia, Saunders, 1987, Figure 286-1.

	Viral	*Bacterial*	*Parasitic*
General:			
Winter, No fecal PMN			
Children	Rotavirus		
Youths, adults	Norwalk-like virus		
Fecal PMN, fever		*C. Jejuni*	
		Shigella	
		Salmonella	
Day care center	Rotavirus	*C. Jejuni*	*Giardia*
	(If < 1-2 yo)	*Shigella*	*Cryptosporidium*
		Salmonella	
Special (footnoted):			
1. Abd. pain, fever (Appendicitis-like)		*Yersinia*	
2. Blood, no fecal PMN		*E. coli* 0157	*Entamoeba*
3. Seafood/coast Exposure	Norwalk-like virus	*Vibrio* species (TCBS agar)	
4. Recent antibiotics		*C. difficile* Cytotoxin	
5. Chronic (> 10d) with weight loss			*Giardia* *Cryptosporidium*
6. Traveler or resident in tropics	+/-Norwalk-like +/-Rotavirus	Enterotoxigenic *E. coli*	*Giardia* *Cryptosporidium*

(fecal PMN usually absent, if present, see above)			+/-*Strongyloides* +/-*Entamoeba*
7. Food/water poisoning			
Nausea, vomiting (inc. per. < 6h)		*S. aureus* *B. cereus*	Anisakis
Diarrhea (no fecal PMN)		*C. perfringens* *B. cereus* ETEC, Vibrios	*Giardia*
Colitis		*Salmonella* *Campylobacter* *Shigella*	
8. Homosexual male:			
Proctitis (distal 15 cm)	HSV	*N. gonorrhoea* *C. trachomatis* *T. pallidum*	
Colitis (> 15 cm)		*C. jejuni*, CLO *Shigella* *C. trachomatis* (LGV) *C. difficile*	Entamoeba
Enteritis (no PMN)			*Giardia*
9. Enteric Infections in immunocompromised hosts:			
Candida	+ Rotavirus Coxsackievirus CMV/HSV Adenovirus	Salmonella Mycobacterium Listeria, CLO C. difficile	Cryptosporidium Strongyloides Giardia Ameba

more than 50% of cases in hospital based studies.[8] While most individuals acquire some degree of immunity to the few serotypes of rotavirus infection, older children and adults remain susceptible to one or another of the Norwalk-like viruses that characteristically cause "winter vomiting disease" that has been seen with high attack rates in families, schools, camps, and with uncooked shellfish ingestion.[9] Such illnesses may involve acute nausea and vomiting or crampy abdominal pain, noninflammatory diarrhea, and lowgrade fever that is usually self-limited over one to three days.

In contrast, patients of any age presenting with fever, tenesmus, abdominal pain and particularly if blood or fecal neutrophils are seen in the stool, have the greatest chance of having *Campylobacter jejuni, Shigella,* or *Salmonella* infection. While these can occur at any time of year, the peak seasons for these infections are usually in the summer or early fall months. Another increasingly recognized common problem arises with diarrheal illnesses in day care centers, which can be due to viral, bacterial, or parasitic causes as noted in the figure.[10-12] Children under the age of two years commonly have rotaviral infections, those with inflammatory diarrhea may have *Shigella,* or *Campylobacter,* or even *Salmonella* or other infections. Noninflamma-

tory diarrhea, particularly if prolonged beyond 5 or 10 days, is increasingly associated with *Giardia* or *Cryptosporidium* infections.[11-13]

Special situations suggesting likely etiologies. A number of specific clues can be obtained from the initial history of a patient presenting with diarrhea that may warrant special consideration of one or more of a number of less commonly diagnosed enteric infections. Although abdominal pain is a common and nonspecific manifestation of many enteric infections, its persistence as the predominant symptom, especially when associated with fever, or an appendicitis-like presentation, should prompt consideration of mesenteric adenitis that is sometimes caused by *Yersinia enterocolitica* or *Yersinia pseudotuberculosis* infections. *Y. enterocolitica* is associated with watery or inflammatory diarrhea in young children and with erythema nodosum and other immunologic manifestations in older adults. An appendicitis-like syndrome has been well recognized with *Y. enterocolitica,* especially among older school children.[14,15] Exposure to a sick dog or cat has also been associated with *Yersinia* infections. Such a presentation should prompt the physician to alert the laboratory to culture for *Yersinia* either from routine culture media or from specialized media such as Cefsulodin-irgasan-novobiocin (CIN) agar or incubation at 25°C or cold enrichment.[16]

Although relatively infrequent, bloody diarrhea without evidence of fecal leukocytes should lead one to suspect either amebiasis (in which the neutrophils are destroyed by the parasite *E. histolytica*[17] or infection with the Shiga-toxin producing "enterohemorrhagic" *E. coli* (EHEC) 0157.[18] The latter may be suspected as a sorbitol-negative *E. coli* in patients with bloody diarrhea.

A patient presenting with diarrhea after ingestion of poorly cooked seafood should prompt a request that the laboratory culture for *Vibrio* species on thiosulfate citrate bile salt-sucrose (TCBS) agar because a number of species may cause either watery or inflammatory diarrhea as well as Norwalk-like viruses.[19] The recent ingestion of antimicrobial agents prior to the onset of a diarrheal illness may have a profound effect on normal colon flora and lead to increased susceptibility to a number of enteric infections. This has been increasingly appreciated with *Salmonella* infections, and is clearly important in the overgrowth of cytotoxin-producing *Clostridium difficile,* the major recognized cause of antibiotic associated pseudomembranous colitis. While cytotoxigenic *C. difficile* colitis is usually self-limited when the antimicrobial agents are discontinued, the persistance or worsening of illness, particularly when antimicrobial agents cannot be stopped, may warrant more specific etiologic definition by examining for *Clostridium difficile* cytotoxin

in the stool or consideration of metronidazole or vancomycin therapy. This has even been suspected in an outbreak of diarrhea in a day care center.[20]

Noninflammatory diarrheal illnesses that persist beyond 10 days, especially when associated with weight loss, should prompt consideraton of *Giardia* or *Cryptosporidium* infection which can be diagnosed by stool ova and parasite examination. The clinician should alert the laboratory to look especially for these small protozoan parasites, which, in the case of *Cryptosporidium,* are best seen with an auramine and modified acid-fast stain.[21]

Travel to tropical areas increases the risk of acquiring an enterotoxigenic *E. coli* infection as well as viral (including Norwalk-like and rotavirus), parasitic (e.g., *Giardia, Entamoeba, Strongyloides,* and *Cryptosporidium*) infections that may be expected to cause noninflammatory diarrhea. In addition, an inflammatory process should prompt consideration of the invasive bacterial pathogens noted above.

Outbreaks of diarrheal illness should prompt a careful history of exposure to define the potential source of the outbreak as well as its incubation period. Outbreaks of enteric illness due to food or water-borne infectious agents or their toxins are usefully divided by the type of illness and incubation period.[22] If the incubation period is less than six hours and especially if the illness is predominantly one of upper abdominal pain, nausea, and vomiting or diarrhea, prompt consideration of *S. aureus, B. cereus,* or *Anisakas* should be considered and appropriate food, vomitus and fecal samples should be saved for special toxin testing if epidemiologically indicated. Fortunately, these illnesses tend to be very brief, and specific diagnosis rarely contributes to effective therapy, which is supportive with attention to fluid and electrolyte balance. Endoscopy for removal of *Anisakas* larvae may be necessary in this infrequent helminthic infection, often occurring after ingestion of uncooked fish with viable larvae. Noninflammatory diarrhea with an incubation period of six to 48 hours suggests *C. perfringens, B. cereus,* enterotoxigenic *E. coli, Vibrio,* or *Giardia* infection and *Salmonella, Campylobacter,* or even *Shigella* infection for inflammatory illnesses. If diarrheal illnesses remain unexplained and only *E. coli* are found on fecal cultures, one may consider saving these organisms for enterotoxin, invasiveness, or adherence testing as well as serotyping and stools should be saved frozen for rotavirus and stool plus paired sera for Norwalk-like virus testing in major outbreaks.

As with food poisoning, enteritis in homosexual males can be usefully subdivided on clinical grounds.[23] Sigmoidoscopy should distinguish proctitis in the distal 15 cm only (caused by herpes virus, gonococcal, chlamydial, or

syphilitic infections) from colitis (with *Campylobacter, Shigella, C. difficile,* or lymphogranuloma venereum chlamydial infections) or noninflammatory diarrhea (often due to giardiasis) in this setting.[23]

Finally, immunosuppressed hosts should have a wide range of viral, bacterial, fungal and parasitic enteropathogens considered.[24] Recognized viral enteric infections in immunocompromised patients include those with cytomegalovirus, herpes simplex virus, coxsackie virus, and rotaviruses.[25] Intracellular bacterial pathogens that are particular problems in patients with impaired cellular immunity include *Salmonella, Mycobacterium avium-intracellulare,* and *Listeria monocytogenes* infections. While a large number of fungal infections may involve the gastrointestinal tract, *Candida albicans* is a particularly common cause of esophagitis or enteritis. Finally, depressed cellular immunity is associated with particularly severe infections with *Cryptosporidium* as well as *Strongyloides* and occasional *Entamoeba histolytica* infections. Despite its frequency, giardiasis does not appear to pose special problems in patients with impaired cellular immunity, but is the only enteric infection clearly documented in patients with impaired secretory immunoglobulin (IgA) production.

Special Diagnostic Tests

Enzyme immunoassays (ELISA) have been developed for rotavirus. Initial problems with specificity, especially in neonates,[26,27] as well as goat milk exposure have been considerably resolved by using blocking tests for confirmation. More recently, a monoclonal enzyme immunoassay has been developed (Pathfinder, Inc.) that seems to be both highly sensitive and specific (Table II).[28] The cost of this test, when it can be run in large numbers ($>$ 50 per test) is approximately $200 for 50 tests plus technician time, approximately four hours for 50 tests (it can be performed in as little as 1½ hours). Equivocal results may require repetition with and without blocking antibody. Consequently, the cost would range from $8 to more than $40, depending on the frequency with which the test is ordered in a given laboratory. This cost is not usually justifiable, because noninflammatory diarrhea in small children, especially during winter months (likely due to rotavirus), tends to be self-limited and require oral rehydration or other fluid and nutritional supportive therapy. While some have suggested that screening infants and young children admitted to hospital wards for rotavirus infection may help to cohort those infected for separation from noninfected patients, up to 50% of healthy neonates may be infected by rotaviruses asymptomatically

and such cohorting is rarely of practical value. Finally, a latex agglutination assay has also been developed (Rotalex) which is also highly sensitive, but less specific (61%) than the ELISA methods (Table II).[28]

The diagnosis of *Clostridium difficile* enterocolitis is best suspected in a patient who develops diarrhea (particularly if inflammatory) while or shortly after taking an antimicrobial agent. Most antimicrobial agents have been incriminated and cephalosporins, broad spectrum penicillins, and clindamycin lead the list. The diagnosis is made by sigmoidoscopy to document the presence of pseudomembranous colitis. Etiology is best confirmed by testing the stool directly for the presence of *C. difficile* cytotoxin, for which tissue culture bioassay using stool filtrates and confirmation using anti-*C. difficile* cytotoxin antiserum remains the most sensitive and specific method to date (Table III). Although the titer of *C. difficile* cytotoxin is not well correlated with severity of disease, noncytotoxigenic *C. difficile* may be isolated, and culture of the organism is both time consuming and less sensitive and specific than looking for the cytotoxin itself. A counterimmunoelectrophoresis method has been developed for stool cytotoxin that is more rapid than tissue culture. However, both its sensitivity and specificity are less than 60%, thus severely limiting its usefulness even as a screening test.[29] Finally, a latex agglutination method has been developed by Marion Scientific Laboratories that is claimed to detect toxin A, although this is currently debated.[30] Whatever the antigen being detected, our experience is that this correlates reasonably well, when present, with cytotoxin as detected by tissue culture. However, its sensitivity, especially for lower titers of cytotoxin, in vitro, falls below 50% (Table III).[29] Consequently, we are left with the tissue culture assay as the most sensitive and specific method to date for detecting *C. difficile* cytotoxin in fecal specimens.

Table IV shows optimal standard methods to detect enteric parasites most clearly associated with diarrheal illnesses. Prompt saline wet mounts may reveal motile trophozoites of *Giardia lamblia* or *Entamoeba histolytica.* Iodine or trichrome stained fecal or small bowel aspirate samples (or Enterotest® string samples, Hedeco, Palo Alto, California) require careful study for the characteristic morphology of *Giardia lamblia* or *Entamoeba histolytica* cysts or trophozoites. Because of frequent errors in both over and under-diagnosis of *E. histolytica* infection, experienced observers and a micrometer eye piece for calculation of trophozoite and cyst sizes are imperative for the reliable diagnosis of *E. histolytica* infection. While a sugar or other flotation method has been suggested for concentration of *Cryp-*

TABLE II. COMPARISON OF ASSAYS FOR ROTAVIRUS

	Sensitivity	*Specificity*
EM (44/100)	100%	100%
Rotazyme II	73	88
NIH EIA	57	96
MC EIA (Pathfinder)	95	95
Latex AG (Rotalex)	98	61

Adapted from reference 28.

TABLE III. COMPARISON OF ASSAYS FOR C. DIFFICILE CYTOTOXIN[32]

	Sensitivity	*Specificity*
Tissue culture (20/67)	100%	100%
CIE	55	58
Latex agglutination	50	96

TABLE IV. OVA AND PARASITE EXAM FOR AGENTS THAT CAUSE DIARRHEA

Saline and iodine wet mounts	Giardia
PVA—trichrome	Amebae
Formol—ethyl acetate auramine/acid fast	Cryptosporidium
Baermann funnel gauze	Strongyloides

tosporidium cysts, a combination of auramine and modified acid-fast stain of formalin and ethyl acetate fixed concentrated specimens seems best for detection of *Cryptosporidium.*[21,31,32] Finally, the Baermann funnel gauze method adds significantly to the detection method for *Strongyloides stercoralis* larvae.[33]

Rapidly approaching practicality is the application of new tools in molecular biology, single stranded,[32] P-labelled nucleic acid sequences as probes for complementary plasmid or bacteriophage DNA sequences that encode virulence traits. As sequences larger than 20 nucleotide bases are generally considered unique, either larger segments from restriction endonuclease digestion or smaller, oligonucleotide probes can be used with remarkable success to detect the heat-labile or heat-stable enterotoxins of *Escherichia coli, Shiga* toxin, the enteroinvasivness plasmid in invasive *E. coli* (EIEC) or *Shigella* and enteroadherence factors (EAF) as shown in Table V.[34-37] Al-

TABLE V. GENE PROBES NOW AVAILABLE FOR DIAGNOSTIC TESTING OF VIRULENCE TRAITS OF DIFFERENT TYPES OF ENTERIC *E. COLI* PATHOGENS

LT (LT-A, LT-B)
LT-like toxin
STa (STh, STp)
STb
Shiga toxin
EIEC (140 Md plasmid)
EAF

though currently limited by need for radioautography or scintillation counting of ^{32}P-labelled probes, biotin-avidin immunoassays are currently being developed.

New Preventive Strategies

There are a wide range of potentially effective preventive strategies that range from such behavioral changes as hand washing to vaccines based on genetic engineering.[36] Examples include the new live Ty-21A typhoid vaccine, streptomycin dependent, and other *Shigella* vaccines and toxoid-producing live cholera vaccines as well as the new toxoid (B subunit) *Vibrio* vaccine that has recently been proved efficacious.[39] Most directly relevant to diarrheal illnesses in the United States, however, are two live, attenuated rotavirus vaccines: live attenuated, bovine, serogroup 1 rotavirus, RIT4237 (Smith Kline), and a monkey kidney cell cultured rotavirus (serogroup 3, developed at the National Institute of Health. As summarized in Table VI, two prospective studies have documented an efficacy of 82 to 88% reduction in rotavirus diarrhea in two placebo-controlled trials of 190 and 347 children, respectively, in Finland.[40-42] This vaccine strain, derived from the NCDV strain of bovine rotavirus and passed in primary bovine kidney and primary monkey kidney cells, is related to subgroup 1 human rotaviruses, and was not associated with constitutional symptoms, elevated leukocyte counts, or excretion of live rotavirus in stools of vaccinated infants less than one year of age. Most previously nonimmune infants developed increases in serum antirotaviral antibody titers. Because of the frequency of rotavirus diarrhea in this setting, these studies suggest that this Smith Kline RIT4237 rotavirus vaccine significantly reduces heterologous rotavirus infections in infants less than one year of age, and even reduces the overall incidence of clinically significant diarrhea lasting more than 24 hours.[40,41] After two doses this efficacy appears to be holding up into a second season

TABLE VI. EFFICACY OF LIVE ATTENUATED ROTAVIRUS VACCINE RIT 4237, BOVINE SEROGROUP 1
ROTAVIRUS DIARRHEA/TOTAL DIARRHEA/NUMBER OF CHILDREN
(% ROTAVIRUS DIARRHEA/TOTAL DIARRHEA)

	Attack rates for placebo	*Vaccine*	*Efficacy (in RV diarrhea)*
1 dose, year 1	18/28/92 (19.6/30.4%)	2/8/86 (2.3/9.3%)	88%
2 doses, year 1	26/36/160 (16.3/22.5%)	5/9/168 (3.0/5.4%)	82%
2 doses, year 2	6/10/160 (3.8/6.3%)	1/8/168 (0.6/4.8%)	84%

Adapted from references 43, 44, 45.

as well. Based on reported attack rates of rotavirus diarrhea accounting for 8 to 52% of community and hospital cases during winter months and assuming an 80% efficacy, this vaccine might be expected to reduce community and hospital cases of diarrhea in young children in industrialized countries by as much as 6 to 40%, respectively. In developing areas this could conceivably translate to a 2 to 3% overall reduction in diarrhea morbidity and a 6 to 10% reduction in childhood mortality under the age of five years.[43]

Cost and Effectiveness of Oral Rehydration Therapy

As noted above and in the algorithm, the vast majority of cases of diarrhea can be treated very effectively with an oral glucose-electrolyte solution. Taking advantage of the intact, sodium-coupled glucose absorption, oral rehydration therapy can reduce hospital admissions for diarrhea by 50 to 60%, hospital case fatality rates by 40 to 50%, cost of treatment or visits to treatment centers, weight loss with diarrhea and even overall diarrhea mortality.[44] The approximate cost of oral rehydration therapy has been estimated to be $1 per case treated and $200 to 300 per death prevented in the developing world.[45] In addition to the intact absorption of D-hexoses and precursors (glucose, galactose, maltose, and starch—the latter broken down by brush border enzymes at the site of absorption with a minimal osmotic burden), neutral aminoacids are also absorbed, independently coupled to sodium. Consequently, new "Super ORT" solutions using rice powder or glycine (or alanine, leucine, or di- and tripeptides gly-gly, gly-ala, leu-gly, or gly^3) are being studied. Preliminary evidence suggests that these may actually reduce the net stool output, a feat that even effective standard oral rehydration therapy had not accomplished. Successful oral rehydration solution com-

TABLE TABLE VII. SUCCESSFUL ORAL REHYDRATION SOLUTIONS

	Per liter
Sodium chloride	3.5 g
Trisodium citrate dihydrate (or $NaHCO_3$—2.5g)	2.9 g
Potassium chloride	1.5 g
Glucose	20 g
Sucrose	40 g
Rice powder	50-80 g
Glycine	8.4 g

positions are listed in Table VII. Such solutions are highly effective, inexpensive, stimulate faster recovery of brush border enzymes, and avoid much of the need for more costly and risky hospitalization and intravenous rehydration therapy.

SUMMARY

The most cost-effective as well as effective approach to definitive etiologic diagnosis and appropriate treatment also helps to identify specific high risk groups that might benefit from newly developing diagnostic studies, vaccines, or treatments. Specific diagnostic tests such as those for rotaviruses, *Clostridium difficile* cytotoxin and increasingly recognized parasites such as *Cryptosporidium,* as well as more traditional culture methods, can be selectively applied in specific settings to aid substantially in etiologic diagnosis. A promising vaccine is the new oral rotavirus vaccine. Oral rehydration therapy is highly effective for the vast majority of acute diarrheal illnesses, especially if delivered early, may prevent worsening dehydration in industrialized countries as well as developing countries around the world and thus prevent much of the need for hospitalization and more costly and risky intravenous rehydration therapy.

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