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Verotoxin -producing Escherichia coli Old Bug New Infections

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Abstract:*EnteropathogenicEscherichia coli first discovered in the last century from the fecal flora of neonates.E.coli resides in human and animal intestine as normal flora.ETEC,EPEC and,EHEC strains cause severe potentially fatal disease . ETEC strains are important cause of childhood diarrhea in developing countries .EPEC infections are acquired by person to person and in the hospitals .EHECs Shiga producing strains that induce bloody diarrhea lead to HUS include renal failure microangiopathic haemolyticanaemia and thrombocytopenia.Vero toxin (Shiga like toxin) can directly damage renal and endothelial cells. The reservoir of EHEC strains is the gastrointestinal tract of young cattle and herbivorous mammals. Low infectious dose of EHEC strains facilitates the transmission of infection. Treatment of EHEC with antimicrobials have not shown clinical benefit rather cause increased production of toxins. Prevention of TD consists to avoid dietary indiscretions, hand washing before eating and eating only cooked food in endemic countries.*

Key Words:*ETEC,EPEC,EHEC, Vero toxin, Pathogenic E.coli.*

I. Introduction

Escherichia coli or Bacterium coli was first isolated from the fecal flora of neonates and named for Theodore Escherich who performed pioneering studies in 1885[I].A gram negative bacilli which commonly occurs as short rods from 2-3 microns long and 0.6 micron in breadth. Most E.coli strains reside harmlessly in the lumen of colon and seem to be poorly adapted to cause disease in healthy adults, there exists aplethora of pathotypes that can cause specific type of illness in both in normal hosts and those with compromised nonspecific defense mechanisms .E.coli exhibits tremendous versatility in its ability to cause disease and the mechanisms by which it does so. Pathogenic strains differ from commensal organisms in that they produce virulence factors specific for each pathotype,which may be encoded by bacteriophages ,or plasmids ,or on stretches of chromosomes known as pathogenicity islands.Most pathogens have larger genomes than do the non-pathogenic strains. It is estimated that total "pangenome" of *E.coli* consists of more than 13000 genes [2,3].*E.coli* can cause diarrhea by no less than six different mechanisms, each displayed by a pathotype with characteristic virulence determinants that contribute to its pathogenic mechanisms [4].The pathogenesis of enterotoxigenic*E.coli*(ETEC) infection as it is understood involves mucosal adherence and toxin-mediated fluid secretion[5].Enteropathogenic*E.coli* (EPEC) strains are defined by the characteristic attaching and effacing effect that they illicit on interaction with epithelial cells and by the fact that they do not produce Shiga toxins [6].Typical EPEC strains carry a large EPEC adherence factor plasmid that encodes bundle-forming pili (BFP) and ability to form micro colonies on tissue culture, a pattern called localized adherence[7,8].Enterohemorrhagic*E.coli* (EHEC) and other Shiga toxin producing *E.coli* are related bacteriophage- encoded cytotoxins that block protein synthesis and induce host cell death[9]. The best known of these strains is 0157:H7, but non-0157 strains cause an estimated 36,000 illnesses, 1000 hospitalization and 30 deaths in the United States yearly [10]. Food safety specialists recognize "Big Six" strains 026,045,0103,0111,0121,and 0145 [10].Enteroaggrevative*E.coli* (EAEC) may be considered a true emerging infection, both because of its relatively recent recognition and because of apparent increase in its importance in some settings. EAEC strains first recognized as cause of diarrhea in 1987 [11]. Enteroinvasive*E.coli* (EIEC) strains are very similar to *Shigella*strains in terms of clinical features and pathogenesis [12]. There are other*E.coli* strains associated with diarrhea.This paper reviews the background, pathogenesis, public health importance, treatment and prevention of ETEC, EPEC and EHEC strains.

II. Enterotoxigenice. coli

Background: ETEC strains are a common and important cause of childhood diarrhea throughout the developing world and a leading cause of diarrhea in travelers who visit these countries [13].Outbreaks may also occur in developed countries.ETEC infections are acquired through ingestion of heavily contaminated water or food and thus result from a failure of sanitation. Infections caused by ETEC range from symptomatic carriage to severe diarrhea-like illness. The predominant symptoms, is watery diarrhea, which may be accompanied by nausea and cramps. Vomiting, severe cramps and fever are not prominent and the stool does not contain blood,

mucus, or fecal leukocytes. The incubation period ranges from a few hours to 2 days and symptoms usually last less than 5 days [14].

.**Pathogenesis**of ETEC infection as it is currently understood involves mucosal adherence and toxin mediated fluid secretion. The genes encoding the toxins and many of genes encoding the adhesions are found on plasmids [15].The pili of ETEC are known as colonization factors (e.g.VFAI,CFA111) or coli surface antigens (e.g.C53,CS6).These appendages include classic chaperone-usher type pili;thinner, more wiry chaperone-usher type fibrillae;and type IV pili.Some strains express afimbrial factors that are not associated with detectable organelles.More than 20 of these pilus- related factors have been described. Strains of ETEC that produce several such factors at a and strains that produce none of the known factors are common [16,17].The diversity of colonization that may be expressed by ETEC strains is thought to be a major factor that allows children in developing countries to have multiple bouts of ETEC diarrhea.According to this theory, adults in developing countries are protected from illness after repeated exposure to multiple ETEC strains during lifetime, whereas travelers to such countries are susceptible. Recently a secreted protein, EtpA, produced by many but not all ETEC strains, was demonstrated to be important for colonization in a murine model, to bind to tips of flagellae, and promote adherence to intestinal cells [18].

III. Enteropathogenice.coli

Background: Typical EPEC strains carry a large EPEC adherence factor plasmid that encodes bundle-forming pili (BPF) and ability to form micro colonies on tissue cells, a pattern called localized adherence [19].EPEC strains were first identified as the cause of devastating outbreaks of nosocomial and community acquired neonatal diarrhea in the 1940s,but such outbreaks are now rare in the developed world.However,EPEC remain a leading cause of severe diarrhea among infants in developing countries [7].Furthermore,atypical EPEC strains lacking BFP are emerging as an important cause of diarrhea among children in developed countries [20].EPEC infections appear to be acquired principally by person- to- person spread and hospitals continue to be a source of infection [21].Infections caused by EPEC are difficult to differentiate from those with other causes: symptoms include watery diarrhea sometimes accompanied by low-grade fever and vomiting. However, EPEC infection may be severe, vomiting may make oral rehydration difficult, and life threatening dehydration may ensue. The disease caused by EPEC may be protracted, resulting in weight loss, malnutrition and death [22, 23]

Pathogenesis: The histological hallmark of EPEC infection, the attaching and effacing effect, involves the intimate attachment of bacteria to the apical surface of intestinal epithelial cells accompanied by the loss (effacement) of microvilli and the formation of cuplike pedestal composed of actin and other cytoskeletal proteins upon which the bacteria rest [24].The attaching and effacing effect is directed by a 41-gene pathogenicity island known as the locus of enterocyte effacement that encodes a T3SS, a toxin secretion system, mainly the effector proteins. Additional effectors trans- located into host cells by T3SS are encoded outside the locus of enterocyte effacement [25, 26,].Typical EPEC strains, which possess an EPEC adherence factor plasmid that encodes EFP, may be more pathogenic than atypical EPEC strains. Both the EPEC adherence factor plasmid and BFP have been demonstrated to be virulence factors .Because BFP aggregate into rope like bundles and expression of BFP is associated with reversible auto aggregation of bacteria in culture and localized adherence,BFPs are believed to mediate the initial adherence to and subsequent dispersal of bacteria from the intestinal surface.Additionally, some BFP also bound to host cell glycoconjugates containing *N*-acetyllactosomine [27, 28].The mechanism by which EPEC strains cause diarrhea is not fully understood. In fact there is several factors may be involved, including loss of microvillus surface area,loosening of tight junctions and direct fluid secretion[29]..

IV .Verotoxin-Producinge.coli

Background:Vero toxin producing *E.coli* are also called*Enterohemorrhagic**E.coli* or Shiga toxin producing *E.coli* strains .These strains are related bacteriophage-encoded cytotoxins that block protein synthesis and induce host cell death. Strains that produce shiga toxins can cause disease of varying severity, including watery diarrhea, bloody diarrhea,haemorrhagiccolitis, haemolytic-uremic syndrome (HUS) and death [30].Among Shiga toxin-producing *E.coli* (STEC) strains,those that share with EPEC strains the ability to induce the attaching and effacing effect encoded by the locus of enterocyte effacement pathogenicity island are known as enterohemorrahagic*E.coli* (EHEC).EHEC strains,especially those belonging to serotypes 0157:H7 have been responsible for larger outbreaks of infection, have higher rates of complication and seem to be more pathogenic than non-EHEC STEC strains.[31].Many researchers recognize other six strains;026,045,0103,0111,0121 and 0145. [10].EHECs that induce bloody diarrhea lead to HUS in 10 % of cases. The clinical manifestations of post diarrhea HUS include renal failure microangiopathic hemolytic anemia and thrombocytopenia. The Verotoxin (Shiga- like toxin) can directly damage renal and endothelial cells. Thrombocytopenia occurs as platelets are consumed by clotting .Hemolytic anemia results from intravascular fibrin deposition, increased fragility of red

blood cells and fragmentation [32].The reservoir of EHEC strains is the gastrointestinal tract of young cattle and other large herbivorous mammals, but these strains can survive for long periods in the environment even at low pH and can proliferate in vegetables and other foods beverages. Outbreaks are often linked to the consumption of undercooked ground beef or from produce, but can arise from a wide variety of other food sources, drinking and recreational water, or petting Zoos and directly person –to person contact [31, 33].].Low infectious dose of EHEC strains,estimated to fewer than 100 organism, no doubt facilitates the transmission of the organism.EHEC infections are manifest by the onset of severe abdominal cramping, which may progress to watery and bloody diarrhea. The frequent absence of fever and appearance of frank hemotochezia can divert the clinician toward considering non-infectious diagnoses such as intussusception in children, inflammatory bowel disease in young adults, and ischemic bowel in elderly [34,35].EHEC infection is the primary cause of HUS and the leading cause of renal insufficiency in children, which may occur in 5 % to 10 % of individuals during EHEC outbreaks and is often heralded by high leukocytosis. Children younger than age 5 year and the elderly are more likely than those between the age extremes to develop HUS. HUS carries a 12 % risk of death or end-stage renal disease, and 25 % of survivors experience long term renal sequelae such as hypertension, proteinuria, and renal insufficiency [36].

Pathogenesis: The main virulence factors of STEC strains are a group of relatedcytotoxinscalled Shiga toxins.Stx1 is virtually identical to toxin produced by *Shigelladysentriae* type 1,and Stx2 share a high degree of sequence similarity and identical functional features. Shiga toxins are encoded on temperate bacteriophages [37]..Importantly; these bacteriophages are induced and lyse the *E.coli*strains that harbor them when cells are stressed by various conditions, including exposure to certain antibiotics [38,39].As a result ,high levels of Shiga toxins are released .Shiga toxins are five identical B subunits that bind to globotriaosylcermideglycosphingolipids (the same receptor used by P fimbriae and parvovirus B 19) The single catalytic A subunit after endocytosis and retrograde transport to endoplasmic reticulum ,catalyzes the depurination of a specific adenine residue in the 28S ribosomal RNA ,rendering the ribosome non-functional. Dissemination of the toxin from the gastrointestinal tract throughout the bloodstream may be facilitated by binding to leukocytes [40-42].Endothelial cells are susceptible to intoxication and may be the most relevant target cells in EHEC-induce HUS. Endothelial cell intoxication is believedto result in increased expression of procoagulants and sub-sequent micro vascular thrombosis[43,44].In addition to Shiga toxins, EHEC,strains (but not –non-EHEC STEC strains) harbor the locus of enterocytes effacement pathogenicity island and are capable of inducing the attaching and effacing effect .Mutation of gene encoding intimin from an 157:H7 EHEC strain resulted in reduced colonization of neonatal piglets but did not affect neurological complications, which are manifestations of Shiga toxin [45-47].STEC infection should be suspected in any patient with grossly bloody diarrhea and should be considered in any individual with diarrhea and cramps. The diagnosis of infection with STEC is vital because of the importance of recognizing potential outbreaks and of taking action to prevent further infections [48].

V. .Pathogenic E.coli Species Associated With Diarrhea

E.coli strains that adhere to tissue culture cellsare associated with diarrhea, especially in older children [43].These strains like EAEC are quite heterogonous and perhaps some are more pathogenic than others [44].In addition to E.coli,the genus Escherichia coli contains several other species including Escherichia blattae,*Escherichia* ferugsonii,and *Escherichia vulneris*,but these are rarely isolated from human infections.Researchers in Bangladesh reported a strain *Hafnia alvei* from infants with diarrhea with pathogenic properties similar to those of EPEC.Further DNA studies revealed that these strains although biochemically similar to *H.alvei*,actually belonged to the genus Escherichia coli and a new species name,*Escherichia albertii*, was proposed [45,46].

VI . Treatment and Preventions

Antibiotics are of questionable value and have not shown to be of clear clinical benefit. Antibiotics that interfere with DNA synthesis, such as fluoroquinolones,have been shown to induce the STX-bearing bacteriophages and cause increased production of toxins{36].Attempts to block toxin production with antibacterial which target ribosomal protein synthesis are conceptually more attractive, plasma exchange offers a controversial but possibly helpful treatment. The use of anti-motility agents (medications that suppress diarrhea by slowing bowel transit) in children under 10 years age or in elderly patients should be avoided, as they increase the risk of HUS with EHEC infections [32].Breast feeding has long being appreciated due to highly protective against EPEC infection.[49,50]..Risk of traveler's(TD) diarrhea can be reduced but not eliminated by educating the traveler to avoid dietary indiscretions.. Antibiotic prophylaxis for TD with a quinolone or with rifampicin has been demonstrated to be effective in many settings. Most guidelines do not recommend prophylaxis for typical traveler because of potential adverse drug effects while away from medical care and because effective rapid onset therapy is available for diarrhea should it occur [51].Antibiotics are used in animal feed to enhance growth selects for resistant bacteria that then colonize humans through food chain. Glycopeptides in animal feed is

linked to vancomycin resistan tbacteria in humans [52,53]. Sensible use of antibiotics in humans and animal is imperative.

V11 .Conclusion

Vero toxin producing EHEC strain and its role in causing bloody diarrhea that lead to HUS is confirmed. Outbreaks are linked to the consumption of undercooked ground beef or produce, but can also arise from a wide variety of other food. Inaddition Shiga toxin producing EHEC strains harbor the locus of enterocytes effacement pathogenicity. STEC infection should be suspected in any patient with grossly bloody diarrhea and should be considered in any individual with diarrhea and cramps.

References

[1] Shulman ST,FriedmanHC,SimsRH,TheodoreEscherich:the first pediatric infectious diseases physician ?. ClinInfec Dis.2007;45:1025-1029.

[2] Welch RA,BurlandV,Plunkett 111 G,et al .Extensive mosaic structure revealed by the complete genome sequence of uropathogenicEscherichia coli.ProcNatlAcadSci USA.2002;99:17020-17020.

[3] RaskoDA,RosovitMJ,MyersGS,et al.The pangenome structure of Escherichia coli: comparative genomic analysis of E.coli commensal and pathogenic isolates. Bacteriol.2008;190:6881-6893.

[4] Levine MM,Nalin DR ,Hoover DI,et al.Immunity to enterotoxgenicEscherichia coli. InfectImmun.1979;23:729-736

[5] ElsingorstEA,WeitzJA.Epithelial cell invasion and adherence directed by the enteroroxigenicEscherichia coli locus is associated with a 104 kilo Dalton outer membrane protein..InfectImmun.1994; 62:3463-3471.

[6] KaperJB.DefiningEPEC.RevMicrobiolsao paula.1996;27(Suppl1):130-133.

[7] GironJa.Donnenberg JP Ms,Martin WC, et al.Distribution of bundle forming pilus structural gene (bfpA) among enteropathogenicEscherchiacoli.I Infect Dis.1993;168:1037-1041.

[8] GriviotoA,GrossRJ,ScotlandSM,et al. An adhesive factor found in strains of Escherichia coli belonging to the traditional infantile enteropathogenicserotypes.Curr MIcrobiol.1979; 3:95-99.

[9] Griffin PM,Ostroff SM,TauxeRV,etal.Illnesses associated with Escherichia coli 0157:H7 infections a broad clinical spectrum Ann Intern Med.1988109:705-712.

[10] Zach Malove (26 April 2010) "Lawyer Battles FSSIS on Non-0157 E.coli(http://www.foodsafety.com/2010/04/marler-seeks-great-e.coli-regulation}."Food SafetyNews.June 2011.

[11] NataroJP,KaperJB,Robins Browne R,et al.Patterns of adherence ofdiarrheagenicEscherichia coli to HEp.2 cells.Pediatric Infect Dis J.1987.6:829-831

[12] MaurelliAT,FernandezRE,BlochCA,at al. "Black holes" and bacterial pathogenicity: a large genomic deletion that enhance the virulence of Shigellaspp and enteroinvasive Escherichia coli.ProcNatlAcadSci USA.1988;95:3943-3948.

[13] NataroJP,KaperJB.DiarrheagenicEscherichia coli.ClinMicrobiol Rev.1998;11:142-201.

[14] Betty ME,AdcockPM,SmithSW,et al. Epidemic diarrhea due to eterogenicEscherichiacoli.Clin Infect Dis.2006;42:329-334.

[15] TausekM,GorrelRJ,StrungellRA,et al. Identification of a protein secretory pathway for secretion of heat- labile enterotoxin by an enterotixigenic strain of Escherichia coli.ProcNatlAcadSci USA.2002;99:7066-7071.

[16] ElsinghorstEA.EnterotoxigenicEscherichia coli.In:Donnenberg MS, et al.Escherchiacoli:Virulence Mechanism of a versatile Pathogen.San Diego: Academic Press.2002:155-187.

[17] SteinslandH,Valentiner-Branth P, Perch M,et al. enterotoxigenicEscherichia coli infections and diarrhea in a cohort of young children in Guinea-Bissau J. Infect Dis.2002;186:1740-1747.

[18] Roy K, Hilliard GM,HamiltonDJ,etal.EnterotoxigenicEscherichia coliEtpA mediates adhesion between flagella and host cells.Nature.2008.

[19] KainKC,BertelukRI,KellyMT,et al. Etiology of childhood diarrhea in Beijing ,China.JClinMicrobiol.1991;29:90-95.

[20] AfsetJE,BevangerI,RomundstadP,etal.Association of atypical enteropathogenicEscherichia coli (EPEC) with prolonged diarrhea .J.Med Microbiol.2004;53:1137-1144.

[21] Paulozzi LJ, JohsonKE,KamaheleLM,etal. Diarrhea associated with adherententeropathogenicEscherichia coli in an infant and toddler Centre, Seattle, Washington.Pediatrics.1986;77:296-300.

[22] Gomes TAT,Rassi V, Macdonald KL,et al. Enteropathogens associated acute diarrheal disease in urban infants in SaoPaulo,Brazil.J. Infect Dis.1991;164:331-337

[23] Rothaum R, MacAdamAJ,Giannella R , et al. A clinicopathological study of enterocyteadherentEscherichia coli: a cause of protracted diarrhea in infants.Gasteroenterol. 1982;83:441-454.

[24] Staley TE Jones EW,Corley ID .Attachement and penetration of Escherchia coli into intestinal epithelium of the ileum in new-born pigs. Am J Pathol.1969,56:371-392.

[25] McDaniel TK,JarvisKG,Donnenberg MS, et al. A genetic locus of enterocyte effacement conserved among diverse enterobacterial pathogens .ProcNatlAcadSci USA.1995;92:1664-1668.

[26] Iguchi A ,ThomsonNR,OguraY,et al. Complete genome sequence and comparative genome analysis of enteropathogenicEscherichia coli 0127:H6 strain E 2348/69.J Bacteriol.2009;191:347-354.

[27] Gomes TAT,VieraMAM,Wachsmuch IK, et al. Serotype specific prevalence of Escherichia coli strains with EPEC adherence factor genes in infants with and without diarrhea in Sao Paulo, Brazil.J Infect Dis.1989;160:131-135.

[28] Hyland RM, Sun J, Griener TP, et al. The bundling pilin protein of enteropathogenicEscherchia coli is an N-acetyllactosamine specific lectin.Cell Microbiol.2008;10: 177-188.

[29] Arnadia KR ,Fagundes-Neto U,ScalestkyIC,Evaluation of multiplex PCRs for diagnosis of infection of diarrheagenicEscherchia coli andshigellaspp.JClin Microbiol.2004;42:5849-5853

[30] Griffin PM,Ostrof SM,Tauxe RV,et al.Illnesses associated with Escherichia 0157:H7 infections: a boroad clinical spectrum.*Ann inern Med*.1988;109:705-712.

[31] Bell BP,Goldoft M,Griffin PM,et al. A multistate outbreak of Escherichia coli 0157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers:the Washington experience.JMA.1994;272:1349-1353.

[32] Woo KB,YounKL,Min SC, et al." A Case of Hemolytic Uremic Syndrome Caused by Escherichiacoli0104:H4"(//weww.ncbi.nlm.nih.gov/pmc/articles/PMC2688167/)..2006;Yonsei Med J 47(3):437-439.

[33] Grump Ja, Sulka Ac, Langer AJ,et al.An outbreak of Escherichia coli 0157:H7 infections among visitors to a dairy farm.N Engl J Med.2002;347:555-560.
[34] Tilden Jr, Young W, McNamara AM, et al. a new route of transmission for Escherichia coli: infection from dry fermented salami. Am J Public Health.1996;86:1142-1145.
[35] Griffin PM, Tause RV. The epidemiology of infections caused by Escherichia coli 0157:H7, other enterohemorrhagicE.coli and the associated haemolytic uremic syndrome.EpidemiolRev.1991;13:60-90.
[36] Garg AX, Suri RS Barrowman N, et al. Long term renal prognosis of diarrhea associated hemolytic uremic syndrome- a systematic review, meta-analysis and meta regression.JAMA.2003;290:1360-1370.
[37] O' Brien AD, Newland JW, Miller SR, et al. Shiga- like toxin converting phages from Escherichia coli strains that cause hemolytic colitis or infantile diarrhea.Science.1984;226:694-696.
[38] Zhang XP, McDaniel AD, Wolf LE, at al. Quinolone antibiotics induceshiga toxin encoding bacteriophages, toxinproduction and death in mice .(http://www.ncbi.nlm.nih.gov/pubmed/10669353} J Infect Dis. 2000:18:664-670.
[39] Jacewicz MS, Mobassaleh M, Gross SK, *et al*. Pathogenesis ofShigella diarrhea:XV11.A mammalian cell membrane glycolipid, Gb3, is required but not sufficient to confer sensitivity to Shiga toxin. J Infect Dis. 1994; 169:538-546.
[40] Te Loo DM, van Hinsbergh VW, van den Heuvel LP, et al. Detection of Vero toxin bound to circulating polymorph nuclear leukocytes of patients with hemolytic uremic syndrome. AmSoc Nepherol.2001;12:800-806.
[41] Germani Y, Begaud E, Duval P, et al. Prevalence of enteropathogenicenteroaggrevative and diffusely adherent Eschericia coli among isolates from children with diarrhea in New Caleidonia. J Infect Dis.1996;174:1124-1126.
[42] Czeczulin JR, Whitman TS, Henderson IR, et al. Phylogenetic analysis of enteroaggrevative and diffusely adherent Escherichia coli .Infection Immun. 1999.67:2692-2699.
[43] Perna NT, Mayhew GF ,Posfai G, et al .Molecular evolution of a pathogenicity island from enterohemorrhagicEscherichia coli 0157:H7.Infect Immune. 1998;3810-3817.
[44] Tzipori S, Gunzer F, Donnenberg MS, et al. The role of each gene in diarrhea and neurological complications in agnotobiotic piglet model of enterohemorrhagicEscherichia coli infection .Infect Immun. 1995;63:3621-3627.
[45] Yoshida T, Fukada M, Koide N, et al. Primary cultures of human endothelial cells susceptible to low doses of Shiga toxins and undergo apoptosis. J Infect Dis.1999; 1680:2048-2052.
[46] Chandler WI, Jelacic S, Boster DR, et al. Prothrombotic coagulation abnormalities preceding the hemolytic-uremic syndrome. N Engl J Med.2002; 346:23-32.
[47] Albert MJ, Faruque SM, Ansaruzzaman M, et al. sharing of virulence associated properties at phenotypic and genetic level between enteropathogenicEscherichia coli and Hafniaalvei.J Med Microbiol1992; 37:310-314
[48] Huys G, Cnockaert M, Janda JM, et al. Escherichia albertiispnov,adiarrheagenic species isolated from stool specimens of Bangladeshi children. IntJ SystEvolMicrobiol2003; 53:807-810.
[49] Blake PA, Ramos S, Macdonald KI ,et al. Pathogen-specific risk factors and protective factors for acute diarrheal disease in urban Brazilian infants. J Infect Dis1993; 167:627-632.
[50] Gamara LM, Carbonare SB, Silva MLM, et al .Inhibition of enteropathogenicEscherichia coli (EPEC) adhesion to Hela cells by human colostrum detection of specific sIgA related EPEC outer membrane protein .Int Arch Allergy Immunol.1994;103:307-310
[51] Fallow S.Molecular Koch's potulates applied to microbial pathogenicity.Rev Infect Dis.1988;10(Suppl2):S274-S276..
[52] Kunin CM .Resistance to Antimicrobial drugs: a worldwide calamity .Ann Intern Med 1993; 118-:557.
[53] Wegener HC,et al. Use of antimicrobial growth promoters in food animals and Enterococcus faecium resistance to therapeutic antimicrobial drugs in Europe. Emerg infect Dis1999; 5 : 329.