current concepts in the management of gram-negative bacterial infections

Current concepts in

the management of gram-negative bacterial infections

Proceedings of an Excerpta Medica Symposium held in Montreal, Canada, April 10, 1973

Editor

Allan R. Ronald

Associate Professor of Medical Microbiology and Medicine
University of Manitoba
Winnipeg, Manitoba, Canada

1974

Excerpta Medica Amsterdam
American Elsevier Publishing Co., Inc. New York

International Congress Series Number 318
ISBN Excerpta Medica 90 219 0247 8
ISBN American Elsevier 0444 15103 6
Library of Congress Catalog Card Number 73-90933

Publisher

Excerpta Medica
Jan van Galenstraat 335
Amsterdam
P.O. Box 1126

Sole distributor for the U.S.A. and Canada

American Elsevier Publishing Company, Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Printed in The Netherlands by Dijkstra Niemeijer, Groningen
Typeset by Pecasse-Eurozet, Maastricht

Introduction

During the past fifteen years gram-negative bacilli have replaced the gram-positive coccal organisms as the most common infectious cause of mortality. This shift has been particularly noticeable in the hospital environment with its optimal epidemiologic setting for the spread of these organisms. Also, whereas in the past gram-positive infections tended to occur in healthy patients, gram-negative pathogens are occurring predominately in the neonate, the elderly, the debilitated and the immunologically compromised patient. The reasons for these changing patterns of bacterial infection are many. Perhaps most important is the widespread use of antibiotics and their alteration of normal flora. Fortunately the advent of serious gram-negative infections has been accompanied by the development of potent antimicrobial agents directed against these organisms. The cephalosporins, carbenicillin, and the aminoglycosides, kanamycin and gentamicin have been life saving in these infections.

With this background it was apropos to review the current status of our understanding of gram-negative infections. On April 10, 1973, nine Canadian and two American antimicrobial investigators assembled in Montreal for a symposium on this subject. The day commenced with a discussion on pediatric gram-negative infection. Dr. George McCracken reviewed his experience with neonatal sepsis in Dallas, Texas, and emphasized the significant mortality of gram-negative sepsis and meningitis in the neonate. Dr. Melvin Marks summarized his studies in gastroenteritis at the Montreal Children's Hospital and updated the audience on recent developments in the pathogenesis of diarrheal disease. Dr. Roland Shapera, Montreal, discussed two childhood gram-negative pathogens, *Hemophilus influenzae* and *Neisseria meningitidis*. The discovery of effective immunizing carbohydrate antigens for both these serious bacterial pathogens is exciting.

The second session concerned itself with surgical and respiratory gram-negative infections. Dr. Martin Lerner, Detroit, succinctly summarized his very many contributions to our knowledge of gram-negative pneumonias. Dr. Jack Mendelson, Montreal, discussed some of the more common causes of post-operative fever and provided illustrative examples from his practice. One of the major developments in infectious diseases in the last decade has been an increased appreciation for the significance of anaerobic bacteria in infections. Dr. George Goldsand, Edmonton, in a beautifully illustrated paper showed conclusively that anaerobes were the major pathogen in a variety of infections.

The next three papers discussed life threatening gram-negative bacteremic infections. Dr. Hugh Robson, Montreal, outlined the pathogenesis and clinical features of the syndrome of 'septic shock'. From his vantage point as an intensive care physician, Dr. Bryan Kirk, Winnipeg, reviewed the various therapeutic modernities available to manage these critically ill patients. Finally Dr. Marc Gurwith, Winnipeg, tabulated the antimicrobial sensitivities of gram-negative pathogens and suggested therapeutic regimens in patients with underlying disease.

The final two papers dealt with urinary infection and antimicrobial aminoglycoside pharmacology. Dr. Ronald, Winnipeg, reviewed current concepts in the therapy of bacterial infection. Dr. Mahon, Toronto,

outlined the pharmacology of kanamycin and gentamicin and provided guidelines for monitoring patients.

This symposium was made possible by a grant from the Schering Corporation of Canada Limited. The participants appreciated the excellent organizational ability of Excerpta Medica both in the conference and in compiling these proceedings.

Dr. A R. Ronald

Contents

I Pediatric infections

George H. McCracken Jr *

*The changing pattern of neonatal bacterial infections: therapeutic considerations***

The etiologic agents of neonatal bacterial diseases have changed over the past 3 decades. In the late 1940's coliform organisms replaced the group A β-hemolytic streptococcus, which had predominated in the previous decade, as the major cause of neonatal septicemia and meningitis. This pattern was changed temporarily in the late 1950's when nosocomial disease with phage group I coagulase positive *Staphylococcus aureus* occurred in obstetrical and nursery units across the country. Over the past decade, *Escherichia coli* and group B β-hemolytic streptococci have been the two most common etiologic agents.

The explanation for this changing pattern of neonatal bacterial infections is unknown. However, there are several possibilities. First, the increased use of antimicrobial agents may exert selective pressure on development of resistant organisms such as penicillinase-producing staphylococci or kanamycin-resistant coliform organisms. In addition, the use of broad spectrum drugs encourages emergence of *Pseudomonas* species and *Candida albicans* due to suppression of the normal gastrointestinal bacterial flora. A second possibility is a change in the antigenic characteristics of bacteria which may in turn alter the virulence of the pathogen. Third, infection with relatively non-virulent 'water bugs' has occurred in many nursery and intensive care units because of increased use of fomites of infection such as respiratory equipment, catheters and moist oxygen. With increasing use of specialized equipment to monitor severely ill infants, the incidence of hospital-acquired infection has increased. A fourth possibility is alteration of host immune mechanisms. For example, passively acquired immunity to specific bacteria may have changed as a result of variations in the antigenic experience of women during the childbearing years. Although there are no data to directly confirm or refute these speculations, it is possible that one or more of these factors are operational in the changing pattern of neonatal bacterial pathogens.

Sepsis neonatorum

Sepsis neonatorum is a disease of infants less than 1 month of age who are clinically ill and have positive blood cultures. The presence of clinical manifestations distinguishes this condition from the transient bacteremia observed in some healthy neonates. Most infants with septicemia present with non-specific signs and symptoms which are usually first noted by the nurse or mother rather than the physician. The most common of these vague signs are altered temperature (hypothermia or fever), lethargy and poor feeding. The presence of temperature elevation above 100°F is significant in the neonate; it is unusual to note fever above 102°F. Signs and symptoms in some infants may suggest respiratory or gastrointestinal disease such as tachypnea and cyanosis or vomiting, diarrhea and abdominal distention.

Group B β-hemolytic streptococci and coliform organisms, particularly *E. coli*, are

* Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, Texas, U.S.A.
** This work was supported by a grant from the John A. Hartford Foundation, Inc.

the most common causative organisms. Familiarity with the historical experience of one's own nursery or intensive care unit is invaluable in guiding selection of antimicrobial therapy for suspected bacterial disease.

The group B β-hemolytic streptococci are the most common gram-positive bacteria isolated from blood of infants with septicemia. The epidemiology, pathogenesis and clinical features of group B streptococcal disease have only recently been defined (Franciosi et al., 1973). The organism is a common inhabitant of the female genital tract and can be isolated from cervical cultures of 5% to 30% of asymptomatic pregnant women. The same organism can be isolated frequently from urethral cultures of the sexual partners of these culture positive women suggesting venereal transmission (Franciosi et al., 1973). Although the great majority of infected pregnant females will have normal, healthy infants, a certain small percentage of pregnancies will result in either stillbirths or infants with neonatal disease.

Group B streptococcal infection of the neonate produces two distinct clinical diseases: an acute septicemic form and a delayed meningitic form. The onset of illness in the septicemic form is usually within the first 12 hours of life and presents as acute respiratory distress with or without shock. Chest roentgenogram usually reveals an aspiration pneumonitis. The pathogenesis of this form of disease is most likely on the basis of aspiration of infected amniotic fluid or cervical secretions at the time of delivery. Cultures from multiple sites reveal group B streptococci indicating generalized colonization of the infant prior to or at the time of delivery. The mortality rate in the fulminant disease is approximately 60 to 80%.

The delayed meningitic form of disease presents at approximately 2 to 12 weeks of life and is indistinguishable from other forms of meningitis during this period. Group B streptococci are grown from cultures of blood and cerebrospinal fluid and the mortality rate is 15 to 30%. The pathogenesis is uncertain, but failure to culture the organism from the maternal cervix suggests that the pathogen in some infants is acquired from nursery personnel or other sources.

Antimicrobial therapy Once septicemia is suspected, suitable cultures should be obtained and therapy started immediately, using ampicillin and either kanamycin or gentamicin. Ampicillin is admistered intravenously or intramuscularly in a dosage of 50 mg/kg/day divided in 2 doses for infants under 1 week and 100 to 150 mg/kg/day divided in 3 doses for infants 1 to 4 weeks of age. The selection of an aminoglycoside antibiotic should be based upon antimicrobial susceptibility studies of coliform organisms isolated from infants in each nursery. Kanamycin is the drug of choice for initial treatment of infections caused by susceptible gram-negative organisms and is administered intramuscularly in a dosage of 15 mg/kg/day in 2 doses for infants under 1 week and 15 mg/kg/day in 2 or 3 doses for infants 1 to 4 weeks of age. However, kanamycin-resistant *E. coli* have been encountered recently in some nurseries in North America (McCracken, 1971). The emergence of coliform bacteria resistant to the aminoglycosides is not unexpected and emphasizes the importance of surveillance programs in nursery units in order to detect changes in susceptibilities. In these nurseries or when an isolate from an infant is shown to be resistant to kanamycin, gentamicin sulfate should be used in the place of kanamycin. The dosage of gentamicin is 5.0 mg/kg/day in 2 doses to infants under 1 week and 7.5 mg/kg/day in 3 doses for infants 1 to 4 weeks of age. All infants receiving aminoglycoside antibiotics should be followed carefully for signs of renal toxicity (cylinduria, hematuria, and elevation of serum creatinine).

When the type of skin lesion or historical experience suggests the possibility of *Pseudomonas* infection, carbenicillin with or without gentamicin is the drug of

choice. For infants under 1 week of age, carbenicillin is administered intravenously or intramuscularly in a 'loading' dose of 100 mg/kg; premature infants should receive 75 mg/kg every 8 hours for the first week of life, while fullterm infants should receive 75 mg/kg every 6 hours for the first three days of life. The dosage in all infants thereafter is 400 mg/kg/day divided into 4 doses (Nelson and McCracken, pending publication). If gentamicin is to be administered with carbenicillin, the drugs should not be mixed in the same solution and administered intravenously. Polymyxin B sulfate in a dosage of 3.5 to 5 mg/kg/day or colistimethate in a dosage of 5 to 8 mg/kg/day both given in 2 or 3 doses intramuscularly have been recommended for neonatal *Pseudomonas* infections. Although there are no corroborative data, it is our impression that these two agents are not as effective as carbenicillin therapy with or without the addition of gentamicin.

When staphylococcal sepsis is suspected but not proved, parenteral methicillin should be substituted for penicillin because approximately 50% of staphylococci encountered in neonates are penicillin-resistant. The dosage of methicillin is 100 mg/kg/day divided into 2 or 3 intravenous or intramuscular injections in infants under 2 weeks and 200 to 300 mg/kg/day in 4 doses for infants 2 to 4 weeks of age. Although kanamycin and gentamicin possess activity against most staphylococci, these agents cannot be recommended because there are no studies of their efficacy in neonatal staphylococcal disease.

Once the pathogen is identified and its antimicrobial susceptibilities are known, the most appropriate drug or drugs should be selected. As a general rule, kanamycin alone or in combination with ampicillin should be used for susceptible *E. coli* and *Klebsiella-Enterobacter* species, gentamicin alone or in combination with ampicillin for kanamycin-resistant coliform bacteria, carbenicillin with or without gentamicin for *Pseudomonas*, ampicillin for *Proteus mirabilis*, enterococcus, and *L. monocytogenes*, penicillin for group B streptococci and susceptible staphylococci and methicillin for penicillinase-producing staphylococci.

Guidelines for determining duration of therapy in the neonatal period are often lacking because objective evidence of illness may be minimal. Culture of the blood should be repeated 24 to 48 hours after initiation of therapy; if positive, alteration of therapy may be necessary. In the absence of deep tissue involvement or abscess formation, treatment is usually continued 5 to 7 days after clinical improvement. When multiple organs are involved or clinical response is slow, treatment may need to be continued for 2 to 3 weeks.

Neonatal meningitis

Neonatal meningitis is relatively uncommon; the incidence is generally reported to be 0.4 cases per 1000 live births. The disease is seen more commonly in premature infants, males and infants born to mothers with complicated pregnancies and/or deliveries.

The bacteria causing neonatal meningitis are similar to those of sepsis neonatorum. Group B β-hemolytic streptococci and *E. coli* presently account for approximately 60% of all cases (Table 1). The next most common etiologic agent is *Listeria monocytogenes*. This pattern of infection has not changed significantly in the past 10 years in Dallas, Texas.

The signs and symptoms of central nervous system infection are frequently indistinguishable from those associated with neonatal septicemia. Lethargy, feeding problems and altered temperature are the most frequent presenting symptoms and respiratory distress, vomiting, diarrhea and abdominal distention are common findings. Seizures are observed frequently and may be due to direct central nervous system inflammation or may be associated with hypoglycemia or hypocalcemia.

Table 1 Etiologic agents in neonatal meningitis, Dallas, 1966-1972

	1966	1967	1968	1969	1970	1971	1972	Total
Gram-negative pathogens								
Escherichia coli	3	0	3	6	3	3	3	21
Enterobacter	0	0	0	1	1	1	0	3
Salmonella	0	0	1	2	0	0	0	3
Serratia	0	0	0	0	0	1	1	2
Gram-positive pathogens								
Group B streptococcus	0	0	4	1	1	1	3	10
Listeria monocytogenes	2	0	1	2	0	1	1	7
Enterococcus	0	0	0	1	2	0	0	3
Coag. negative staphylococcus	0	0	1	1	0	0	0	2
Total	5	0	10	14	7	7	8	51

Pathogenesis The unusually high frequency of *E. coli* meningitis in neonates has intrigued pediatricians for many years. It has been generally assumed to be a consequence of the neonates' relatively immature and sluggish immune defense mechanisms and failure of maternal macroglobulins bactericidal for coliforms to cross the placenta.

Preliminary studies in collaboration with Doctor John B. Robbins of the National Institutes of Health, Doctor Emil Gotschlich of the Rockefeller Institute and Doctors Ida and Frits Orskov of the E. coli Reference Center in Copenhagen suggest that these *E. coli* are uniquely virulent. Forty-five strains of *E. coli* isolated from cerebrospinal fluid of infants with meningitis were tested for cross-reactive antigens to the capsular polysaccharides of meningococcus groups A, B and C and pneumococcal types I and III. These strains of *E. coli* are from infants of diverse geographic origin. Immunoprecipitants were observed only with the meningococcal group B antiserum. Forty-eight of 59 *E. coli* strains (81%) showed cross-reaction with the group B meningococcal capsular polysaccharide; the specificity of this reaction was demonstrated by absorption of the antiserum with purified group B meningococcal polysaccharide or with the *E. coli* K1 antigen. Of 44 *E. coli* serotyped, the 07, 01 and 018 antigens were most frequently associated with the cerebrospinal fluid isolates. We have been unable to demonstrate this K1 antigen with strains of *E. coli* isolated from blood cultures of septic infants, rectal cultures of normal infants or with enteropathogenic strains of *E. coli*. Further observations indicate that the *E. coli* containing K1 antigen are particularly virulent for mice. When these organisms are inoculated intraperitoneally with a 5% hog gastric mucin adjuvant, the LD_{50} values are uniformly less than 800 organisms and frequently less than 50 organisms. In contrast, the LD_{50} values of K1 negative *E. coli* from cerebrospinal fluid were 800 to 100,000 organisms. Enteropathogenic strains of *E. coli* and *E. coli* from normal babies are considerably less virulent for mice; the LD_{50} values for these organisms were greater than 10,000 organisms.

The significance of these findings is unknown. The specific cross-reaction between the *E. coli* K1 antigen and the group B meningococcal antiserum is due to chemical homogeneity between the two capsular antigens. These two capsular polysaccharides are homopolymers of sialic acid that are neuraminidase-sensitive (Liu et al., 1971). It is likely that this capsular polysaccharide which is related to the invasive characteristics of the group B meningococ-

cus is responsible in some way for the proclivity of these *E. coli* for the central nervous system of neonates. Further studies are under way to define the pathogenesis and epidemiology of neonatal *E. coli* meningitis.

Antimicrobial therapy Therapy of neonatal meningitis should be based in part on the pharmacokinetic properties of antibiotics in neonates with meningitis. Recent studies have shown that 2.5 mg/kg of gentamicin administered intramuscularly produces peak cerebrospinal fluid levels of approximately 2 μg/ml 4 to 6 hours after the dose (McCracken et al., 1971). If 1 mg of intrathecal gentamicin is added to this regimen values as high as 20 μg/ml are observed several hours after instillation. With kanamycin, peak values of 6 to 10 μg/ml are observed 4 to 6 hours after a dose of 7.5 mg/kg. The cerebrospinal fluid levels of ampicillin are higher; peak values of 10 to 30 μg/ml are observed 2 to 4 hours after a 50 mg/kg/dose of ampicillin (McCracken, 1972). From this data it is apparent that the commonly accepted minimal inhibitory endpoints of susceptibility for these antibiotics are frequently greater than the level achieved in cerebrospinal fluid. For example, a strain of *E. coli* with a gentamicin MIC value of 5 μg/ml is considered susceptible when treating blood stream infection, but may be resistant when treating meningitis because peak cerebrospinal fluid gentamicin levels following parenteral therapy are considerably lower than this value. Therefore, changing therapeutic regimens must be considered such as selecting alternative therapy, combining two or more antibiotics, increasing the parenteral dose, or changing the route of administration.

At the present time, ampicillin and gentamicin are recommended for initial therapy of neonatal meningitis. The dosage of ampicillin is 100 mg/kg/day in 2 divided doses during the first week of life and 200 mg/kg/day in 3 doses thereafter. The dosage of gentamicin is the same as for septicemia. All infants should have a repeat spinal fluid examination and culture 24 to 36 hours after initiation of therapy. If organisms are seen on methylene blue or gram stain of the fluid, we currently recommend the instillation of gentamicin intrathecally in a total daily dose of 1 mg. It is then our policy to repeat the lumbar puncture every 24 hours and administer intrathecal medication on a daily or every other day basis until the cerebrospinal fluid is sterile

There is a marked discrepancy in the time necessary to sterilize cerebrospinal fluid of infants with meningitis due to gram-negative organisms compared with meningitis caused by gram-positive organisms (McCracken, 1972). It is not uncommon to have positive cerebrospinal fluid cultures for 5 to 7 days or longer in infants with meningitis caused by coliform bacteria. Persistent bacteriorrhachia in the face of 'appropriate' therapy may be due to failure to achieve effective antimicrobial activity in the central nervous system, sequestration of organisms in the ventricular system or subdural space and/or inadequate host immune mechanisms. If the infant fails to show clinical improvement or bacteria are not eradicated from the cerebrospinal fluid after 4 or 5 days of therapy, diagnostic taps of the subdural space and ventricles should be performed. If ventriculitis is present, drainage is indicated and a suitable antibiotic is instilled into the ventricular system either directly or by way of a reservoir. Gentamicin is the preferred drug for susceptible coliform bacteria and *Pseudomonas*. Following a daily dose of 1 mg, ventricular fluid levels of 4 to 120 μg/ml may be observed (McCracken et al., 1971). The higher values are noted after multiple doses and may represent accumulation of drug in the ventricular system. Duration of intraventricular therapy is dependent upon the clinical condition and the time necessary to sterilize the ventricular fluid.

When neonatal meningitis is caused by group B β-hemolytic streptococci, penicillin G alone should be given intravenously

in a dosage of 100,000 units/kg/day divided in 2 or 3 doses. Ampicillin is the drug of choice for therapy of *Listeria* meningitis. In both these forms of meningitis, cerebrospinal fluid cultures are sterilized promptly.

Parenteral antimicrobial therapy should be continued for approximately 2 to 3 weeks after sterilization of the cerebrospinal fluid. It is usually only necessary to continue therapy for a total of 2 weeks in patients with meningitis due to gram-positive organisms, while longer periods of therapy are necessary in infants with meningitis caused by gram-negative organisms. The patients should be carefully followed for signs of hematologic and renal toxicity.

Summary

The etiologic agents of neonatal septicemia and meningitis have changed over the past 3 decades. Currently group B β-hemolytic streptococci and *E. coli* account for the majority of cases. Familiarity with the historical experience of a nursery and the antimicrobial susceptibilities of the common pathogens of neonatal bacterial disease is essential in selecting initial antibiotic therapy. Ampicillin and gentamicin or kanamycin are the drugs of choice for initial therapy of neonatal septicemia and meningitis. Once the organism has been identified and the susceptibilities determined, the most appropriate drug or drugs should be used. Because of delayed bacteriologic cure in coliform meningitis, instillation of gentamicin intrathecally may be necessary. Duration of therapy is approximately 10 to 14 days for sepsis neonatorum and for meningitis caused by gram-positive bacteria and 3 weeks or longer for meningitis caused by gram-negative organisms.

References

Franciosi, R. A., Knostman, J. D. and Zimmerman, R. A. (1973): Group B streptococcal neonatal and infant infections. *J. Pediat., 82*, 707.

Liu, T. Y., Gotschlich, E. C., Dunne, F. Y. and Jonsson, E. K. (1971): Studies on the meningococcal polysaccharides. II Composition and chemical properties of the group B and C polysaccharide. *J. biol. Chem., 246*, 4703.

McCracken, G. H. (1971): Changing pattern of the antimicrobial susceptibilities of *E. coli* in neonatal infections. *J. Pediat., 78*, 942.

McCracken, G. H. (1972): The rate of bacteriologic response to antimicrobial therapy in neonatal meningitis. *Amer. J. Dis. Child., 123*, 547.

McCracken, G. H., Chrane, D. F. and Thomas, M. L. (1971): Pharmacologic evaluation of gentamicin in newborn infants. *J. infect. Dis., 124 (Suppl.)*, 214.

Nelson, J. D. and McCracken, G. H.: Clinical pharmacology of carbenicillin and gentamicin in the neonate and comparative efficacy with ampicillin and gentamicin. *Pediatrics*. Submitted for publication.

Melvin I. Marks *

The pathogenesis and therapy of gram-negative bacterial gastroenteritis

Gastroenteritis continues to be a major source of morbidity on a world-wide scale. Known bacterial causes account for approximately 25% of infections, viruses for another 25% and the pathogenesis in approximately one half of the cases is unclear. The purpose of this report is to review some of the current concepts of pathogenesis and therapy of the known gram-negative bacterial causes of gastroenteritis. Historical and other perspectives are available in other reviews (Grady and Keusch, 1971*a*, *b*).

Salmonella

Salmonella accounts for approximately 10% of foodborne outbreaks in North America (U.S. Dept. of Health, Education and Welfare, 1972) and an even larger number of sporadic cases (Cherubin, 1973). Recently the problem of turtle-associated salmonellosis was reviewed (Lamm et al., 1972; Altman et al., 1972; Kaufmann et al., 1972) and legislation was enacted restricting the sale of turtles in North America. The ubiquitous nature of salmonellae and the complex host-defense mechanisms involved in the pathogenesis and recovery from salmonella infections make the prevention, control and therapy of this type of gastroenteritis a prodigious task.

We have recently investigated the natural history of non-typhoidal salmonella gastroenteritis in children (Kazemi et al., 1973 *a*). Infection is often associated with severe illness but rarely with complications or death in normal uncomplicated hosts. The carrier state, as measured by excretion of salmonella in the stools, is not prolonged in most children beyond 8 weeks (except in young infants). The pathology of salmonella gastroenteritis includes extensive inflammation of the small intestine (especially the ileum) and at times, the colon, with shallow ulcers and superficial necrosis of intestinal lymphoid tissue. Our studies indicate that bacteremia is frequent although often not symptomatic. There is a delicate balance between the parasite (which is of variable virulence) and host-defense mechanisms which include humoral antibody (Venneman and Berry, 1971 *a*), macrophage activity (Maier and Oels, 1972), secretory IgA, cell-mediated immunity (Venneman and Berry, 1971 *b*) and probably other mechanisms as well. Any alteration in these host-defense mechanisms due to disease, drugs etc., may lead to severe infection and/or increased shedding of bacteria and contamination of others.

Although a number of efforts have been made to immunize animals against salmonella the protection at best is temporary, strain-specific and incomplete (Herzberg et al., 1972; Collins and Carter, 1972). We have studied the role of antibiotherapy retrospectively and prospectively in the treatment of uncomplicated salmonella gastroenteritis and have confirmed the uselessness of this approach (Kazemi et al., 1973 *b*). Morbidity is not shortened and the carrier rate remains the same with or

* Department of Pediatrics (Infectious Disease), McGill University, and Montreal Children's Hospital Research Institute, Montreal, Quebec, Canada

without antibiotics. Others, studying adult infections, have reported the same results or an increase in the duration of carrier states in antibiotic treated patients (Aserkoff and Bennet, 1969). The use of antibiotics has the additional disadvantage of encouraging carriage with resistant strains of bacteria (Schroeder et al., 1968). A new antibiotic combination, sulfamethoxazole-trimethoprim, demonstrated synergism against salmonella in vitro (Marks et al., 1973). A controlled clinical evaluation of this drug and ampicillin in children showed no advantage of antibiotic therapy (Kazemi et al., 1973 *b*). It appears, therefore, that the control of salmonella gastroenteritis requires strict hygienic measures, isolation procedures and food surveillance directed especially at lower socio-economic groups where crowding and person to person spread is more common. Better understanding of defense mechanisms and the intracellular activity of salmonella in the human host will hopefully allow more logical approaches to prevention and treatment.

Shigella

Man is the major host reservoir for shigella and transmission is by the fecal-oral route. Mucosal penetration with microulcers of the colon and, at times, the terminal ileum are seen but perforations and/or bacteremia are rare. Shigella gastroenteritis illustrates certain complexities of host-parasite interactions including the role of enterotoxin in the pathogenesis of diarrhea (Keusch et al., 1972; Formal et al., 1972; Gemski et al., 1972; Levine et al., 1973).

Although cholera will not be discussed in detail, studies of its pathogenesis have led to the discovery of exotoxins (enterotoxins) produced by gram-negative bacteria capable of causing enterosorption (influx of fluid and electrolytes into the lumen of the bowel) without damaging mucosal epithelial cells to a significant degree (Carpenter, 1971). Enterotoxin is produced by certain shigella (Levine et al., 1973), cholera (Carpenter, 1971), *Escherichia coli* (Etkin and Gorbach, 1971) (indistinguishable from normal fecal flora) and some gram-positive bacteria associated with gastroenteritis. The ingestion of the toxin and/or bacteria producing it, or the induction of host flora to produce this toxin may account for a significant amount of gastroenteritis in humans (South, 1971). Many gram-negative bacteria are capable of conjugating and transferring genetic information from cell to cell which can direct enzymatic production of enterotoxin in previously nontoxin-producing strains (Skerman et al., 1972). Preliminary clinical studies to confirm the importance of enterotoxin in gastroenteritis have yielded conflicting results (DuPont et al., 1971; Gorbach and Khurana, 1972). If enterotoxin could be detected readily and neutralizing substances developed or protective immunogenic mechanisms described, relatively easy avenues for therapy and prevention of the bulk of gastroenteritis could be available.

Shigella dysenteriae have provided models to investigate the relative importance of bacterial invasiveness and toxin production in the pathogenesis of gastroenteritis (Gemski et al., 1972; Levine et al., 1973). Mutants have been produced which can either invade colonic mucosal epithelial cells or produce enterotoxin. Recent studies with these mutants have reemphasized the role of invasion and have demonstrated that enterotoxin is not essential for the production of shigellosis although it may be for cholera and some *E. coli* gastroenteritis.

The prevention of shigellosis in institutions by vaccination is under investigation (DuPont et al., 1972*a*,*b*; Levine et al., 1972). These studies have emphasized the importance of local (gastrointestinal) antibody and penetration of mucosal cells in protection against shigella gastroenteritis. Two candidate bacteria, a streptomycin-dependent strain and a mutant hybrid, look promising. However, the prospects for community application of such vaccines are slight.

The therapy of shigella gastroenteritis is

controversial (Tong et al., 1970; Haltalin et al., 1972). Although it is clear that antibiotic treatment of shigella gastroenteritis is effective in shortening the clinical course of illness and the shedding of shigella in the stools, development of antibiotic resistant strains is a limiting factor (Ross et al., 1972). *Shigella sonnei* and *flexneri* have become increasingly resistant to ampicillin in many areas. Whether this is due to the treatment of shigellosis with ampicillin, or due to the widespread indiscriminate use of penicillins for upper respiratory infections, for example, is unclear. Nevertheless it appears wise to restrict antibiotic treatment of shigella gastroenteritis to hospitalized patients and/or those severely ill and at high risk. Antibiotherapy is only of secondary importance to strict hygienic measures and isolation procedures.

Escherichia coli

Escherichia coli can cause gastroenteritis by invasion and cell penetration (like salmonella and most shigella) or by enterotoxin production (like cholera and some shigella) (South, 1971; DuPont et al., 1971). Enterotoxin production may be an important mechanism for the pathogenesis for *E. coli* gastroenteritis for both enteropathogenic strains and strains indistinguishable from normal host flora. No practical means for detection of such cases and/or prevention and therapy have yet been described. A specific antigen (adhesive antigen) coating certain *E. coli* is responsible for attachment to the wall of the small intestine and probably enhances invasiveness and thereby virulence (Jones and Rutter, 1972). *E. coli* is also capable of producing colicin, an antibiotic-like substance which may kill competing bacteria (including other *E. coli*) and also therefore enhance virulence (Ikari et al., 1969). The production of adhesive antigen, colicins, enterotoxins, and antibiotic resistance are all plasmid-associated characteristics capable of being transferred between gram-negative bacteria of the same and differing species. These complex and interrelated mechanisms are probably responsible for the virulence of *E. coli* in the production of gastroenteritis and probably also available to most of the other gram-negative bacteria responsible for gastroenteritis. Careful consideration, therefore, must be given to the parasite as well as the host in considering the pathogenesis of gastroenteritis.

Hygiene is our mainstay for control of all gram-negative bacteria gastroenteritis, including *E. coli*. Antibiotic therapy of *E. coli* gastroenteritis can shorten the illness and excretion of bacteria but is also associated with development of resistance as described above for shigella. Antibiotic treatment should probably be restricted to severe cases and to a short treatment course (Nelson, 1971).

Other gram-negative bacteria

Vibrio parahemolyticus is the primary cause of foodborne (especially shellfish) gastroenteritis in Japan and is being recognized more frequently in North America (Thomson and Pivnick 1972; Dadisman et al., 1973; Peffers and Bailey, 1973). Special bacteriologic media must be used to detect this organism as well as another gram-negative bacterium, *Yersinia enterocolitica*, which has also been described in association with gastroenteritis (Toma et al., 1972; Lafleur et al., 1972). Illness in these patients is usually mild and self-limited and antibiotic therapy is not recommended. Most of the pathogenic mechanisms and preventative measures outlined above for enterotoxin-producing shigella and *Escherichia coli* are also applicable to *Vibrio cholera* gastroenteritis. The use of oral fluid therapy for acute infectious diarrhea has been applied in North America situations after its successful use in cholera (Hirschhorn et al., 1972). Cholera is discussed in more detail elsewhere (Carpenter, 1971; Rosenbaum, 1972; Carpenter and Hirschhorn, 1972; McBean et al., 1972).

In certain circumstances (foodborne outbreaks, sewage poisoning and animal