Leading articles


*Clostridium sordelli* and antibiotic-associated pseudomembranous colitis

Pseudomembranous colitis is an uncommon complication of antibiotic therapy which may arise as a primary toxic effect or progress from diarrhoea of varying severity. Although this condition was described before the antibiotic era (Billroth, 1867; Finney, 1893) there has been an apparent increase in the incidence in recent years following the introduction of many new antibiotics. Staphylococcal enterocolitis which followed the introduction of the tetracyclines and the prevalence of the strain phage-type 80/81, was the first example of an ‘epidemic’ antibiotic associated colitis (Finland, Grigsby & Haight, 1954). However the new semi-synthetic antibiotics many with antistaphylococcal activity and the decline in the incidence of the specific staphylococcal strain led to a marked reduction in this complication.

The current increase in the number of reports of pseudomembranous colitis appears to be related both to the introduction of lincomycin and clindamycin (Benner & Tellman, 1970; Cohen, McNeil & Wells, 1973; Scott, Nicholson & Kerr, 1973) and a greater awareness and more specialized investigation of patients with gastrointestinal side-effects during or following chemotherapy. The frequency of reports following these two antibiotics has led many workers to refer to ‘clindamycin-associated’ or ‘clindamycin-induced colitis’ implying a direct causal effect. The wide variation in the incidence is puzzling. Tedesco, Barton & Alpers (1974) in a group of 200 patients reported an incidence of diarrhoea of 21% and pseudomembranous colitis of 10%. However many cases were diagnosed early and were mild. On the other hand a report from the manufacturers, Upjohn, estimated the incidence at between 1 in 50,000 and 1 in 100,000 (Hubbard, 1974) patient treatments. It is likely that both of these extremes are inaccurate as the first examined a group of patients with an apparently higher susceptibility to diarrhoea than found by other workers (DeHaan, Schellenberg, van der Bosch & Maile, 1972; Geddes, Bridgwater, Williams, Oon & Grimshaw, 1970; Stiver & Ronald 1971; Leigh, Simmons & Williams, 1977) and the latter as it was based on marketing trials and antibiotic usage where reporting of the complication may be underestimated. Perhaps a more accurate incidence of 1 in 5000 to 1 in 10,000 was made by Ramirez-Ronda (1974). However it is clear that the onset of diarrhoea does not indicate progression to colitis as Leigh & Simmons (1978) found that 39% of patients with diarrhoea recovered normal bowel function whilst still receiving clindamycin.

There is evidence of increasing morbidity but most deaths have occurred in the elderly and otherwise seriously ill patients or where extensive surgery has been undertaken. In many cases the indication or justification for clindamycin or lincomycin therapy is lacking. Pittman, Pittman & Humphrey (1974) in a report of 16 patients with colitis described two physicians who had taken lincomycin for nasal furunculosis and many single case reports describe the indication for therapy as a mild upper respiratory tract infection. In contrast, the treatment of severe anaerobic sepsis has rarely been associated with reports of pseudomembranous colitis (Bartlett, Sutter & Finegold, 1972; Fass, Scholand, Hodges & Saslaw, 1973; Chow, Montgomerie & Guze, 1974; Gorbach & Thadepalli, 1974; Leigh et al., 1977).

The clinical, radiological and histological features of pseudomembranous colitis have been well described (Pittman et al., 1974; Tedesco et al., 1974; Cohen et al., 1974; LeFrock, Klamer, Chen, Gainer, Omar & Anderson, 1975; Tedesco, 1976; Hoberman et al., 1976; Price & Davies, 1977). However there has been controversy regarding its etiology. The important role played by antibiotics is undisputed although in the pre-antibiotic era the condition was associated with recent surgery, intestinal obstruction, malignant conditions particularly leukaemia and lymphoma, and therapy with corticosteroids and opiates (Penner & Bernheim, 1939; Goulson & McGovern, 1965; LeFrock et al., 1975). Idiopathic cases are now rarely seen (Jackson & Anders, 1972) and antibiotic therapy has been considered to be the ‘trigger’ mechanism leading to a combined local Schwartzman phenomenon associated with capillary microthrombi and ischaemia but a secondary stimulus is still necessary for a full explanation (Price & Davies, 1977).

Many theories have been offered for the etiology of pseudomembranous colitis although the analysis of most patients has been retrospective. Using the analogy of staphylococcal
enterocolitis it has frequently been suggested that a change in the faecal bacterial flora was responsible. Marr, Sans & Tedesco (1975) found that while in diarrhoea the anaerobic faecal flora was only slightly reduced, in colitis there was a marked reduction. However Gorbach et al. (1969) and Finegold, Harada & Miller (1965) have shown a reduction of the anaerobic flora following lincomycin therapy and Leigh & Simmons (1978) reported that irrespective of the presence of diarrhoea, clindamycin and lincomycin caused a striking reduction in the total anaerobic bacterial count. Although an altered bacterial flora appears the most plausible explanation the presence of recognized pathogens including Staphylococcus aureus and Candida species has never been reported but few workers have looked carefully at changes in the individual anaerobic species.

Other etiological factors have been reported such as a virus infection (Steer, 1975) but similar viral particles have been found in many other conditions (Pittman et al., 1974; Owen, 1976). Alterations in bile acid and salt metabolism (Hoffman & Poley, 1969; Burbridge & Milligan, 1975) and electrolyte changes have been incriminated and abnormalities of vascular supply and perfusion have been described in pseudomembranous colitis but not when associated with clindamycin (Ecker, Williams, McKittrick & Failing, 1970). Mucosal cell abnormalities have been related to a cellular effect of the antibiotic or toxic bacterial metabolites (Pittman et al., 1974). Stasis of bowel contents leading to a prolonged exposure to the etiological agent has been suggested as the use of drugs such as atropine diphenoxylate (Lomotil) in combination with lincomycin leads to more severe diarrhoea (Novak, Lee, Seckman, Phillips & DiSanto, 1976) and some patients have had pre-existing intestinal disease (Weinrib & Sheehy, 1975). Familial cases have also been described (Harrod, Brown, Weinberg, Harkness & Goldstein, 1975).

Despite all these theories there has been agreement about some of the characteristics of pseudomembranous colitis. Women are more commonly affected and the incidence is higher in the older age groups. Whilst there have been many single case reports, the 'epidemic' nature of outbreaks often in a narrowly defined area has been striking. The incidence is not related to dose or usage and there may be a marked seasonal or annual variation.

The first published evidence for a bacterial cause for pseudomembranous colitis was presented by Larson and his colleagues (1977). These workers reported the case of a 12-year-old girl who developed colitis following a short course of penicillin therapy. Careful examination of the faeces did not reveal any pathogens but a cytotoxic effect was noted in tissue cultures set up for virus isolation after inoculation with a faecal suspension. This effect was confirmed in other patients with pseudomembranous colitis and was only present in the acute stage of the illness. No effect was seen with a faecal suspension from normal patients. The etiological agent was classified as a heat-labile bacterial toxin.

In a more recent paper from America, Rifkin and his co-workers (1977) have also demonstrated the presence of a toxin in the faeces of two patients with pseudomembranous colitis. They found that the toxin was neutralized by specific Clostridium sordellii antitoxin but not by antitoxins prepared from other clostridial strains or enteropathogens. In their hamster model faecal filtrates produced effects which resembled those caused by clindamycin-induced ileocaecitis and pure Clostridium sordellii toxin. Vancomycin was shown to be protective in the hamster model and clinically effective in one of the patients with colitis. The efficacy of vancomycin has previously been reported in the treatment of staphylococcal enterocolitis (Kahn & Hall, 1966).

These two important papers have reported the probable cause of pseudomembranous colitis and a logical explanation for many of the past etiological observations. It is highly likely that there is a cross-infection risk where a patient develops this condition and it is now important that careful detailed bacteriological studies are carried out on the faeces of all patients with both diarrhoea and colitis to confirm the clostridial findings. In addition it would be valuable to know whether patients can be asymptomatic carriers of Clostridium sordellii or whether there is a latent period before the development of colitis symptoms when prophylactic antibiotic therapy would be indicated. The use of combined clindamycin and vancomycin treatment will be suggested but this is inadvisable except where pseudomembranous colitis has developed or the patient is known to be at increased risk.

It is now possible to consider further the role of lincomycin and clindamycin especially in severe anaerobic infection where its wider bacterial spectrum provides a valuable alternative to metronidazole. The high incidence of anaerobic infections mainly complicating gastrointestinal tract surgery suggest that there
is a place for the use of both clindamycin and metronidazole as prophylactic and therapeutic agents.

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References


Billroth quoted by Penner & Bernheim (1939).


**Treatment of Lancefield group B streptococcal infections**

Lancefield group B streptococci (*Streptococcus agalactiae*) are a cause of serious perinatal sepsis, producing both high morbidity and mortality rates (Eickhoff, Klein, Daly, Ingall & Finland, 1964; Franciosi, Knostman & Zimmerman, 1973; Baker, Barrett, Gordon & Yow, 1973). Although uniformly sensitive to penicillin and ampicillin (Finch, French & Phillips, 1976) they require higher concentrations to inhibit growth, than do strains of *Streptococcus pyogenes* (Matsen & Coughlan, 1972).

*Streptococcus agalactiae* is isolated from a wide range of clinical specimens and reports suggest that the increase in isolation rates (Finn & Holden, 1970) is real rather than apparent, following the increased awareness of this particular organism. However, this experience has not been universal (Stokes & Mehtar, 1977).

There appears to have been no change in the susceptibility to penicillin of strains isolated in the past ten years (Baker, Bette & Barrett, 1976) although occasional reports have shown strains producing clinical disease with high MICs of 0-12 mg/l to penicillin (Dormand & Adams, 1976). In addition there has been a series of case reports of recurrent group B streptococcal infection in infants who have received an adequate course of chemotherapy. (Dormand & Adams, 1976; Broughton, Mitchell, Grossman, Hadley & Cohen, 1976; Truog, Davis & Ray, 1976; Walker, Santos & Quintero, 1976).

These reports together with mean mortality rates of 23% and 55% for neonatal group B streptococcal meningitis and septicaemia respectively (Anthony & Okado, 1977), has provided the impetus to investigate possible alternative treatment regimens.

The relevance of *in vitro* methods to determine antimicrobial susceptibility with a fixed inoculum size of about 10^4 organisms/ml, has been questioned (Baker, 1977). There is evidence to suggest that some infants with group B streptococcal meningitis have between 10^10-10^11 viable bacteria/ml of cerebrospinal fluid. By increasing the inoculum size to 10^8 organism/ml the MIC of penicillin is increased to >2-4 mg/l (Baker, 1977); this is close to penicillin levels that can be achieved in the cerebrospinal fluid, with a daily dose of 250,000 units/kg (Baker, 1977).

Antibiotic combinations of a penicillin and an aminoglycoside against a variety of streptococci frequently demonstrate *in vitro* synergism. *Streptococcus agalactiae* is no exception although experience is limited and some of the information conflicting. For example Schauf, Deveikis, Riff & Serota (1977), were only able to demonstrate synergism with clinically achievable levels of ampicillin and gentamicin in two strains. On the other hand these authors also reported some interesting observations from kinetic studies, plotting time-killing curves for ampicillin (1-2 mg/l) in combination with gentamicin (10 mg/l) and have shown a 1-4 log reduction in colony counts after 4 h incubation, compared with results for ampicillin alone. Furthermore the killing rates for ampicillin alone are much slower for group B streptococci than for *Streptococcus pyogenes*, but are usually complete by 18 h incubation.

The clinical relevance of these observations remains to be determined. In an experimental mouse model improved survival and accelerated clearing of bacteremia has been reported, using combined therapy with ampicillin and...