Diphtheria revisited

IN view of recent reports of plague in India and Ebola virus in Zaire, and the confusion these caused over travel to or from the affected countries and over the management of suspected cases arriving in other countries, it is important to highlight another infectious disease that is much more likely to appear in the United Kingdom: diphtheria. Until the introduction of immunization for diphtheria, this disease was a major cause of morbidity and death. In recent years, however, it has re-emerged as an infection risk for international travellers.

Corynebacterium diphtheriae causes throat infections, with formation of a pseudomembrane. Death can result from respiratory obstruction or from the effects of exotoxin on myocardial and neural tissues. This bacterium also causes infections of the skin, causing persistent ulcers; these have been seen, as a result of bites by infected insects, in Britons returning from India, the Yemen and Ghana.[1-3] The virulence of the bacterium is determined by its invasive potential along with its ability to produce toxin. There is no standard measurement of the invasive potential. Toxin production is measured in the laboratory and strains are toxigenic (weak or strong) or non-toxigenic. There are three biotypes of *C diphtheriae*: gravis, intermedius and mitis, with gravis causing the worst infections in the past. Prevalence varies worldwide and in recent decades there has been a decrease in the proportion of toxigenic strains[4] perhaps because of immunization.

Immunization with diphtheria toxoid was introduced in the UK in 1942 and resulted in a dramatic fall from 46 281 cases and 2480 deaths in 1940 to 37 cases and six deaths in 1957. In developing countries it is possible to obtain immunity from subclinical throat infections and skin lesions because the extent of population carriage is high. This is not possible in the UK so a high uptake of immunization is essential. There is debate about the serum levels of antibodies to *C diphtheriae* required for protection,[5] although 0.01 IU ml^{-1} is regarded by most workers as protective.[6] Immunization is routine for infants in the UK but antibody levels wane and a booster dose is advised at school entry.[7]

It has been shown that 15% of Royal Air Force recruits[8] and 23% of Italian army recruits[9] were not immune to diphtheria. Worryingly, van Geldermalsen and Wenning have suggested that in certain parts of the world a moderate uptake of immunization may decrease the carriage of toxigenic strains of *C diphtheriae*, and hence the opportunity to acquire natural immunity decreases, leaving at risk those groups of the population not accessible for immunization programmes.[10] This may account for a diphtheria outbreak in Lesotho in 1989 despite an immunization programme having been established in 1977.

Interest in diphtheria has been rekindled:[11] the major economic and social changes occurring in the former Union of Soviet Socialist Republics, with homelessness and overcrowding, have led to a decrease in vaccine uptake.[12] People's desire to keep a healthy distance from needles because of the risk of acquiring the human immunodeficiency virus has contributed to this decrease. Coverage of diphtheria immunization in Moscow in those aged up to 16 years has fallen to 66%[13] and, coupled with a waning of adult immunity, this has led to a sudden increase in the number of cases of diphtheria: from 1869 cases in 1991 and 3897 in 1992 to 15 211 in 1993.[14] This is the largest outbreak in the developed world since the 1960s,[15] with adults accounting for 65% of fatalities.[13]

Diphtheria was reported in 1993 in two fully immunized teenagers in the UK,[16] and in two imported cases from Italy and Bangladesh in 1994.[17] No cases of diphtheria have yet arrived in the UK from Russia, although a Finnish man returned home from Russia with the disease after attending a party where drinks were taken from shared glasses and he had kissed his local girlfriend.[18] With the former USSR opening up to trade and tourism there may be an increased risk of diphtheria particularly for those undertaking prolonged visits, such as health workers or teachers. Recommendations are that all unimmunized people travelling to the former USSR should have a full course of three doses of vaccine at monthly intervals;[7] previously immunized travellers require a booster only if they intend to live or work with local residents and were immunized more than 10 years previously.

The Joint Committee on Vaccination and Immunization has advised that the routine immunization schedule for children should be augmented to include diphtheria vaccine given at the time of the school-leaving dose of tetanus toxoid.[19] A special low-dose diphtheria toxoid combined with tetanus toxoid is licensed for this purpose. The dose is 0.5 ml by intramuscular or deep subcutaneous injection.

Patients with suspected respiratory diphtheria, characterized by sudden onset of fever, malaise and sore throat together with a thick grey tonsillar exudate, should be isolated in hospital; therapy with antitoxin and intravenous antibiotics (penicillin or erythromycin) should not be delayed until bacteriological confirmation is received. Treatment for suspected cases of cutaneous diphtheria is the same as that for respiratory diphtheria except that antitoxin is seldom required. The disease is notifiable and the local consultant in communicable disease control must be informed of actual or potential cases. Nose and throat swabs from the family and travelling companions of patients with suspected diphtheria, and from health care staff working with confirmed cases, are needed. A booster dose of diphtheria vaccine is indicated for close contacts whose last dose of the vaccine was more than five years previously and a full course of immunization is indicated for those who have not been immunized. All close contacts should receive antibiotic prophylaxis, without waiting for the results of their swabs and regardless of their vaccine status: erythromycin orally for 10 days is recommended, 250 mg four times a day for adults and 40 mg/kg daily in divided doses for children.[6] If swabs from close contacts are positive, they should not be treated with the antitoxin unless the disease develops. Follow-up swabs two weeks after treatment are required from any contact who proved positive in order to confirm eradication.

As always, awareness by the physician of signs and symptoms and the importance of taking a thorough travel history can never be overemphasized.

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Aspirin and acute myocardial infarction: clarifying the message

IT is now well established that aspirin has an important role in the treatment of acute myocardial infarction.[1,2] However, publications have misleadingly stated that the benefits of aspirin therapy are 'a 25% reduction in mortality when 160 mg aspirin was given within the first four hours [of an acute myocardial infarction]'[3] and 'in connection with the use of 150 mg or more being chewed at the time of the acute [myocardial infarction] event'.[4] There are two misconceptions which seem to have arisen in these interpretations of the research findings.[3-5] First, that administering a single aspirin tablet soon after the onset of acute myocardial infarction will lead to a substantial reduction in the risk of death, and secondly, that any delay in the commencement of aspirin therapy will lead to a reduction in its effectiveness. Close scrutiny of the relevant randomized controlled trials suggests that there is no evidence supporting either of these interpretations.

The second international study of infarct survival (ISIS-2) provides evidence of the effectiveness of both aspirin and streptokinase in over 17 000 patients who were randomized on admission to hospital to receive placebo, 160 mg of aspirin daily for four weeks, a one-hour infusion of streptokinase as immediate care or the combination of aspirin and streptokinase.[1] The trial reported statistically and clinically significant reductions in 35-day vascular mortality rates (deaths which were definitely or possibly of a vascular cause) with the aspirin and streptokinase combination compared with either treatment alone, and with either treatment compared with placebo. The fact that the effects of thrombolytic therapy and aspirin therapy were found to be additive suggests that they may act in different ways. Thrombolytic therapy reopens occluded arteries and antiplatelet (aspirin) therapy may perform a complementary role by inhibiting cyclo-oxygenase–platelet activity and preventing further thrombus formation.[6] The exact mechanism by which aspirin exerts its influence is unclear.

There is strong evidence that the effectiveness of thrombolytic therapy depends on the prompt administration of the single infusion, and that its effectiveness reduces with delay.[1,7] Studies have been published that examine the time taken for patients to receive thrombolysis[8,9] and the practicalities and safety of its administration in general practice;[10,11] guidelines have been outlined[12,13] and local policies adopted in attempts to reduce delays.[10]

The policy regarding aspirin therapy should differ from that for thrombolytic therapy. The 23% reduction in the risk of vascular death in the 35 days following myocardial infarction seen in the aspirin treatment arms of ISIS-2 was associated with a four-week course of aspirin and not a single tablet.[1] Research has failed to indicate that administration of a single aspirin tablet at the time of acute myocardial infarction leads to any reduction in mortality.[14] Guidelines on the use of aspirin must reflect the importance of continuing the use of aspirin therapy as a secondary preventive measure,[2] as well as ensuring that aspirin therapy is commenced.

It has also been noted that the participants in ISIS-2 who incurred up to 24 hours' delay in commencing aspirin therapy fared no worse than those who received their first tablet within the first few hours after the onset of symptoms.[15] This contrasts with the findings for thrombolytic therapy. Although the evidence suggests that the commencement of aspirin therapy may not merit the same degree of urgency as commencement of thrombolytic therapy, there is no reason to introduce any delay in its administration, given its relative safety and the ease of administration.[14]

It is unfortunate that several studies assessing the quality of care that general practitioners administer to patients with suspected myocardial infarction have concentrated on assessing the commencement[3-5] rather than the continuation[16] of aspirin therapy. These studies may in part be responsible for disseminating the wrong treatment message. A first requirement of a study which assesses clinical performance is that the procedure under question is of established effectiveness.[17] These studies misinterpret the results of ISIS-2 by wrongly attributing the mortality reduction to the initial aspirin administration.[3-5] It is essential that time is taken to appraise critically and interpret correctly the results of the relevant clinical trials before reviews of performance are undertaken.

Putting the evidence of the treatment of patients with suspected acute myocardial infarction into practice is probably best