Interim UK guidelines for management of close community contacts of invasive group A streptococcal disease

Health Protection Agency, Group A Streptococcus Working Group

Summary: Group A streptococci cause a wide range of illnesses from non-invasive disease such as pharyngitis to more severe invasive infections such as necrotising fasciitis. There remains uncertainty about the risk of invasive disease among close contacts of an index case of invasive disease and whether this risk warrants antibiotic prophylaxis. A 19-200 fold increased risk among household contacts has been reported in the literature. Recommendations for antibiotic prophylaxis regimens vary by country.

A comprehensive literature review together with preliminary analysis of 2003 United Kingdom data from the strep-EURO programme informed the interim recommendations of an expert working group. The evidence base to formulate definitive guidance is weak. Risk calculations based on provisional UK data estimated that over 2,000 contacts would need to receive antibiotic prophylaxis to prevent a subsequent case of invasive group A streptococcal disease. The Working Group considered that currently available evidence did not warrant the routine administration of chemoprophylaxis to all close community contacts. More robust risk estimates will be derived from ongoing UK surveillance data to inform a review of this guidance in 2005.

Key words:
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contacts
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Key recommendations

1. Close contacts of a case of invasive Group A streptococcal disease should receive information outlining the signs and symptoms of invasive Group A streptococcal infection. They should be advised to seek medical attention if they develop such symptoms within 30 days of diagnosis in the index case.

2. Antibiotics should only be administered:
- To mother and baby if either develops invasive group A streptococcal disease in the neonatal period (first 28 days of life);
- To close contacts if they have symptoms suggestive of localised Group A streptococcal infection i.e. sore throat, fever, skin infection;
- To the entire household if there are two or more cases of invasive group A streptococcal disease within a 30 day time period.

3. Oral Penicillin V is the drug of first choice where chemoprophylaxis is indicated. Azithromycin is a suitable alternative for those allergic to penicillin.

Introduction

Definitions

Invasive group A streptococcal disease (iGAS) is defined as an infection associated with the isolation of group A streptococci (GAS) from a normally sterile body site. Three clinical syndromes are described[1,2] (table 1): (i) group A streptococcal toxic shock syndrome differentiated from other types of iGAS infections by shock and multi-organ system failure early in the course of infection (ii) necrotising fasciitis characterised by extensive local necrosis of subcutaneous soft tissues and skin, and (iii) infections characterised by the isolation of GAS from a normally sterile site in patients not meeting the criteria for streptococcal toxic shock syndrome or necrotising fasciitis. Included in this group are bacteraemia with no identified focus and focal infections such as meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, septic arthritis, myositis, and surgical wound infections.

Epidemiology of iGAS

The epidemiology of iGAS is complex. More than 120 different M protein serotypes and/or *emm* sequence types of *S. pyogenes* exist and numerous distinct streptococcal pyrogenic exotoxins (spes) have been described[2,3]. Clinical isolates examined by the Centre for Disease Control and Prevention during the 1970s and 1980s showed a doubling in the prevalence of M1 and M3 serotypes during that time[4,5]. The 1990s have seen an increase globally in the reporting of iGAS consistent with the re-emergence of more virulent strains such as the M1 serotype that in earlier decades was primarily seen in cases of either superficial disease or scarlet fever[6].

Enhanced surveillance programmes were set up in North America and Europe to determine the trends of iGAS within and between countries. A major programme with participation from ten countries is currently underway in Europe (strep-EURO) to enhance the understanding of the epidemiology of iGAS in Europe[7]. Although severe GAS infections are not notifiable in most European countries, estimates based on clinically and bacteriologically documented cases have suggested that during the last decade the iGAS incidence in Europe ranged between one and four cases per 100,000 population per annum[8]. Preliminary results from 2003 UK data show that the incidence of iGAS was 3.8 per 100,000 population[5]. The data thus far also confirmed the rapid and significant mortality associated with these diseases, 20% of cases dying within seven days of diagnosis[9].

Carriage and transmission

Asymptomatic pharyngeal carriage of GAS is common, with prevalence ranging from 5% to 30% of the general population[10]. Person-to-person spread of GAS within families or other closed communities has been widely reported with linked cases of invasive and non-invasive infections[6,11-14]. Family outbreaks have been ascribed to 'ping pong spread', i.e. spread between family members of distinct serotypes[15]. During one 10-month period of study of one family, 13 GAS isolates of four different strains were found each of them being isolated from two or more family members[16].

Risk factors for iGAS

A comprehensive literature review (A Smith, 2004; unpublished) identified risk factors from a prospective population-based active surveillance study[17], a retrospective population-based study[18], a prospective study[19], a case control study[20] and numerous outbreak and case reports[11-14, 21-26].

People at increased risk for sporadic iGAS include those aged over 65 years of age; those who have recently been infected with varicella virus; those with HIV infection, diabetes, heart disease or cancer; and those using high-dose steroids or intravenous drugs.

Evidence Level Range 2+ to 3

TABLE 1 Spectrum of invasive group A streptococcal disease

Diagnosis	Characteristics
Streptococcal toxic shock syndrome	Shock and multi-organ system failure
Necrotising fasciitis	Extensive local necrosis of subcutaneous soft tissues and skin
Other invasive disease	Bacteraemia with/without identified focus of infection

Risk to household contacts

Estimates of risk of subsequent iGAS are uncertain because of the small number of documented 'index case-subsequent case' pairs ($n = 5$) in two studies that have attempted to quantify this risk[26,27]. All five subsequent cases occurred among adults who were immediate family members and all five occurred within three weeks of the index case's date of culture. The increased risk in household members may be due to a combination of genetic susceptibility in the family, close contact with carriers in the family and the virulence of the particular GAS strain involved.

In a follow up study of clusters identified from strep-EURO data in England, Wales, and Northern Ireland during 2003, five household clusters were identified, two wife-husband pairs and three mother-neonate pairs (I Oliver, 2004; unpublished data). Infections in the neonatal period (first 28 days of life) were therefore considered as having a high risk of further cases in the mother or baby. Risk estimates for other household settings suggested that over 2,000 close contacts would need treatment to prevent a case, even assuming 100% effectiveness of chemoprophylaxis.

Background to guidance

Public health policies on the management of contacts of iGAS vary between countries. The Centers for Disease Control and Prevention (CDC) recommend, when chemoprophylaxis has been decided upon, a choice of benzathine penicillin G (one dose by injection) and rifampicin (four days), clindamycin (10 days) or azithromycin (five days) to households where at least one contact is in a high-risk group[28]. Health Canada recommends a 10-day course of cephalosporin, erythromycin or penicillin V to all close contacts[29]. The UK and other European countries do not have published guidance. A postal questionnaire survey of consultants in communicable disease control (CCDCs) was undertaken in England in 2004. There was an 84% response rate from health protection units and it showed that most did not have a local policy for the management of community contacts of sporadic cases (I Oliver, 2004; unpublished data).

TABLE 2 Levels of evidence

1++	High quality meta-analyses, systematic reviews of renadomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted met- analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analysis, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is casual
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is casual
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationshp is not casual
3	Non-anlalytic studies, e.g. case reports, case series
4	Expert opinion

Effectiveness of antibiotic prophylaxis

Antibiotic prophylaxis can eradicate carriage of GAS.
Evidence Level Range 1- to 2++

No clinical trials have evaluated the effectiveness of chemoprophylaxis in preventing iGAS among household contacts of a case. However there are a number of trials that have successfully shown the effectiveness of antimicrobial agents for the eradication of GAS from the upper respiratory tract[30-33]. It is these studies that have formed the basis of Canadian and American recommendations of antimicrobial regimens for the management of contacts of cases of iGAS. The effectiveness of these policies on preventing iGAS is not known.

Objective of guidance

The objective of these guidelines is to present the rationale and recommendations for the public health management of close community contacts of cases of iGAS in the UK. Guidance for hospital settings is not included.

Working group

The Working Group comprised representatives from the Health Protection Agency, the Public Health Medicine Environmental Group, the Infection Control Nurses Association (ICNA) and the Association of Medical Microbiologists.

The Scottish Intercollegiate Guidelines Network (SIGN) system was used to evaluate the levels of evidence[34.35]. An evidence level was assigned (Table 2). A grade of recommendation was then agreed as the considered judgement of the Working Group based on the volume, consistency and generalisability etc. of the evidence (table 3).

Public health action after a community-acquired case

Aim of chemoprophylaxis

Chemoprophylaxis aims to reduce the risk of invasive disease by eradicating carriage of GAS in those contacts at highest risk. It may act in two ways namely: (1) eradicating carriage from established carriers who pose a risk of infection to others, and (2) eradicating carriage in those who have newly acquired the invasive strain and who may themselves be at risk.

Chemoprophylaxis

Definition of a close community contact

Although the risk to contacts is low the highest documented risk is to people who live in the same

TABLE 3 Grades of recommendation

A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

household[26,27]. For pragmatic reasons, the Working Group took the view that close contacts should be defined as for the public health management of meningococcal disease in the UK[36].

A close contact is defined as a person who has had prolonged close contact with the case in a household-type setting during the seven days before onset of illness.

Evidence Level Range 2+

Options for chemoprophylaxis

The working group considered a number of options for prophylaxis:

A. Giving antibiotic prophylaxis to:
   1. All close contacts of a case (as in Canada).
   2. Only to high risk contacts.
   3. All close contacts if at least one contact is at high risk (as in US).
   4. Close contacts who had a positive throat culture.

B. Not giving any prophylaxis but raising awareness of risk.

The following points were considered in reaching a recommendation.

- Antibiotics have potential undesirable side effects (adverse drug reactions, contributing to the development of drug-resistant organisms, changing the normal human body flora).
- The risk of iGAS among household contacts is higher than the risk to the general population, but the risk is low and not accurately quantified.
- The sensitivity of throat swab in detection of carriage is not known. Transmission of GAS may occur between close contacts in the interval between taking a swab and administering antibiotics if positive. Similarly, preventable cases may occur in this same interval.
- Administering antibiotics to high-risk contacts alone does not remove the risk of acquisition from other asymptomatic carriers.
- The identification and administration of antibiotics to all close contacts is undoubtedly a logistical challenge.
- Risk estimates for household settings suggested that over 2,000 close contacts would need treatment to prevent a case, even assuming 100% effectiveness of chemoprophylaxis (I Oliver, 2004; unpublished data).

In light of these considerations the Group came to a view that prophylaxis should not be routinely recommended to close contacts with the exception of cases in mother or baby during the neonatal period, or if individuals have symptoms consistent with localised GAS infection*. A heightened index of suspicion for iGAS in close contacts should be maintained for 30 days after the diagnosis is made in the index patient [11-13, 26,27].

Antibiotics should only be administered: (1) to mother and baby if either develops invasive group A streptoccocal disease in the neonatal period (first 28 days of life); (2) to close contacts if they have symptoms suggestive of localised group A streptococcal infection i.e. sore throat, fever, skin infection.

If contacts have syptoms suggestive of invasive disease, e.g. high fever, severe muscle aches, or localised muscle tenderness, then they should be immediately referred to A&E for emergency assessment.

Other close contacts should (1) receive a GAS information leaflet outlining the signs and symptoms of iGAS disease, and (2) be advised to seek immediate medical attention if they develop such symptoms.

Additional measures to consider in circumstances involving more than one linked patient are described under special situations in section 5.

Reporting of invasive isolate

To facilitate the identification of contacts of index cases all suspected cases of invasive GAS disease should be reported to the relevant CCDC or consultant in public health. Isolates from invasive GAS infections should be

* iGAS informaion leaflet for contacts available at www.hpa.org.uk/infections/topics_az/strepto/gen_info.htm

TABLE 4 Recommended chemoprophylaxis regimens

Choice	Drug	Dose	Duration
1	PenicillinV	250-500mg QID	10 days
2	Azithromycin	12mg/kg/day p.o. in a single dose (max daily dose, 500mg/day)	5 days

forwarded for typing to the relevant National Reference Laboratory (see appendix 2).

Recommended antibiotic regimen

The Working Group has recommended an antibiotic prophylaxis regimen utilising a number of criteria to assist the process: (1) limitations (including applicability) of evidence from trials showing effectiveness of antimicrobial agents in eradication of GAS from the upper respiratory tract[30-33], (2) minimising undesirable side effects, (3) minimising selection for resistant organisms, (4) maximising compliance, and (5) maximising cost effectiveness.

Penicillin has been the drug of choice to prevent acute rheumatic fever following GAS pharyngitis for over 50 years[37,38,39]. It is among the best tolerated and safest antimicrobial agents[40,41]. The cost of oral penicillin V is substantially below that of alternative agents. GAS strains have remained consistently penicillin susceptible[42]. As yet, to our knowledge, there have been no published reports of penicillin-resistant clinical isolates of GAS.

Azithromycin is suitable for those who are allergic to penicillin and where the index case isolate is azithromycin (erythromycin) sensitive. If azithromycin is used for prophylaxis then susceptibility to erythromycin/azithromycin in the index case isolate should be confirmed and changed if resistant. Currently (2003) approximately 3%-4% of iGAS isolates are resistant to these agents so susceptibility is likely but must not be assumed[43]. Azithromycin is active against Group A streptococci and is not subject to degradation by beta-lactamase[44,45]. Total drug exposure after a single daily dose for five days is comparable with that achieved after 10 days of treatment with shorter acting agents[45]. Comparative clinical trials involving azithromycin have demonstrated higher clinical and bacteriological response rates to those achieved with oral penicillin V[33,46,47]. Azithromycin is associated with a higher incidence of gastrointestinal complaints than penicillin V but rates of drug discontinuation from such side effects were low[48]. Azithromycin is preferable to erythromycin because of its spectrum of action, shorter course and fewer gastrointestinal side effects.

Oral Penicillin V (250-500mgs QID for 10 days) is the drug of first choice where chemoprophylaxis is indicated.

Azithromycin (12mgs/kg/day for 5 days) is a suitable choice for those who are allergic to penicillin.

In the unlikely event of an allergy to penicillin and azithromycin then contact the local Consultant Microbiologist to discuss a suitable alternative.

Special situations

Nursing homes

Nursing home residents account for approximately 4% of all cases[27]. Outbreaks of GAS infection in nursing homes have been reported[13,24,25]. Prevention of the spread of iGAS is especially important because of the high mortality rate in this population. Approaches to consider include targeting antibiotic treatment only to those residents and staff who are GAS carriers, or antibiotic treatment of all residents and staff irrespective of GAS colonisation.

Injecting drug users

Injecting drug users are at increased risk of sporadic iGAS[26-27].

Cases of iGAS presenting in hostels providing temporary accommodation for the homeless, can represent a challenge for health teams. In such settings

TABLE 5 Targeted versus mass antibiotic prophylaxis in nursing homes

Targeted antibiotic prophylaxis	Mass antibiotic prophylaxis
Limits antibiotic exposure in residents	Could contribute to development of antibiotic resistance
Cultures may be false negative	Should eradicate all carriage in residents and staff
Could miss transmission by: • Transient carriage • False negatives • Contaminated fomites • Visiting family members	Could miss transmission by: • Contaminated fomites • Visiting family members
Neither approach can compensate for poor infection control practices	

Single case in a nursing home

Nursing homes should review infection control measures and maintain a heightened index of suspicion for 30 days. Close contacts among residents (sharing same room/side ward) and staff should only receive chemoprophylaxis if (a) they have symptoms suggestive of localised Group A streptococcal infection i.e. sore throat, fever, skin infection and (b) a viral URTI has been excluded as the more likely diagnosis.

GRADE D

If close contacts have symptoms suggestive of invasive disease, e.g. high fever, severe muscle aches, localised muscle tenderness, and a viral URTI has been excluded then they should be immediately referred to A&E for urgent assessment.

Two or more cases in a nursing home

Setting up an outbreak control team is advised. Targeted or mass antibiotic prophylaxis for residents and staff should be considered (depending on factors such as interval between cases, epidemiological links, fatality rate). Infection control measures should be reviewed.

GRADE D

it may be appropriate to undertake additional measures to those stated for nursing homes. This should include the formation of an outbreak control team that would consider all the epidemiological information available to formulate the most appropriate proportional response.

Outbreak control team — initial actions

1. Assess carefully all the epidemiological information available: confirmed and probable cases, serotyping, dates of onset, links between cases, size of population containing the cases, homogeneity of population containing the cases.

2. Inform centres with national responsibility for GAS surveillance, investigation and control. As well as providing expert advice they can assist with case finding and may already be aware of linked cases. See Appendix 2 – contact details.

3. Decide on approach, if any, to chemoprophylaxis based on 1 and 2.

4. Communications strategy to provide clear, consistent and accurate information

GRADE D

When iGAS occurs inn injecting drug user populations, local drug action teams should (1) be informed about the clinical manifectations of GS infection (sore throat, fever, skin infection, and/or localised muscle tenderness; (2) disseminate thjis information among injecting drug users; (3) advise injecting drug users to seek medical attention if they develop such symptoms of if they develop unusual skin lesions.

General practioners and accident and emergency departments should be alerted to the occurrence of outbreaks of iGAS among injecting drug users.

GRADE D

Clusters

Household clusters

If two or more cases of iGAS occur in the same household within a 30-day time period then the entire household should receive chemoprophylaxis.

Clusters in the wider community

One of the major difficulties in targeting a wider community for intervention is deciding on the population boundaries, often defined by time frame, geography and social characteristics. The extent of the public health response should be decided at a meeting of an outbreak control team.

Risk communication

The risk of iGAS among household contacts is higher than the risk to the general population, but the risk is low and not accurately quantified. The provision of information to case contacts of iGAS is the cornerstone of any risk communication strategy. Template information leaflets for close community contacts of cases are available on the HPA website (www.hpa.org.uk/infections/topics_az/strepto/guidelines).

Review date

The Working Group will review this guidance by December 2005.

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Appendix 1

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Appendix 2

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Specialist and Reference Microbiology Division
Respiratory and Systemic Infection Laboratory
61 Colindale Avenue
London NW9 5EQ
Out of hours: 020 8200 4400/ 020 8200 6868 (Duty Doctor)

National Public Health Service for Wales
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Abton House
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Cardiff CF14 3QX
Tel: 02920521997

Scottish Centre for Infection and Environmental Health
CliftonHouse
Clifton Place
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G3 7LN
Tel: 0141 300 1100
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Communicable Disease Surveillance Centre Northern Ireland
Belfast City Hospital
Lisburn Road
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Details of local **Health Protection Units** in England and contact personnel can be found on the HPA website at <http://www.hpa.org.uk/lars_homepage.htm>.

Severe Streptococcal Infections and Necrotising Fasciitis Support Foundation
Email: www.nfsuk.org.uk
Tel: 01254 878701
Fax: 01254 878701