UNCERTAINTIES PAGE

Should we screen and decolonise contacts of patients with Panton-Valentine leukocidin associated *Staphylococcus aureus* infection?

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In the past decade *Staphylococcus aureus* associated with a toxin called Panton-Valentine leukocidin (PVL-SA) has emerged worldwide, mainly causing severe skin and soft tissue infections in patients in the community. Multidrug resistant strains have rapidly spread across parts of North America and Australia, resulting in increasingly limited treatment options. In most of Europe surveillance data suggest that PVL associated disease is rare, which may underestimate the role of PVL in mild to moderate skin infections, for which samples for testing are not routinely taken in primary care.

The main strategy to prevent reinfection with or transmission of PVL-SA is stringent hygiene combined with decolonisation treatment. In the United States, where PVL associated strains of meticillin resistant *S aureus* (MRSA) are commonplace, testing for the PVL toxin is not recommended (table). Decolonisation is considered only when standard infection prevention methods have failed, in recognition of the lack of efficacy data to support eradication of *S aureus*.[1] In England the Health Protection Agency advises a relatively aggressive approach to the management of PVL-SA infection, based on the assumption that cases are mainly rare and severe.[2] No international consensus has been reached on whether decolonisation treatment should depend on PVL status, meticillin resistance, or simply the presence of severe and recurrent *S aureus* infection.

What is the evidence of the uncertainty?

We searched PubMed, the Cochrane Library, and the Current Clinical Trials Database to identify randomised controlled trials and systematic reviews that have evaluated the use of screening and decolonisation to prevent the transmission of infection to contacts of either *S aureus* infection or specifically PVL-SA infection. No published randomised controlled trials have evaluated the use of screening or decolonisation treatment among contacts of people infected with *S aureus* or PVL-SA.

A Cochrane review evaluated the use of mupirocin to reduce the rate of infection in people colonised with *S aureus*. Pooled results from the eight included randomised controlled trials showed a significant reduction in the rate of *S aureus* infection with intranasal mupirocin compared with placebo (relative risk 0.55; 95% confidence interval 0.43 to 0.70).[4] These findings suggest that decolonisation may reduce the risk of infection in nasal carriers of *S aureus*, but whether this reduces the transmission of PVL-SA infection in a household setting is unknown.

Currently there is little evidence to support the use of decolonisation or screening for household contacts of people known to have PVL associated infection; however, a pragmatic approach taking account of the severity of disease in the index case may be warranted.

US and English guidance on the management of close contacts of an index case infected with PVL associated *Staphylococcus aureus*

Policy	Health Protection Agency's guidance for England[2]	US Centers for Disease Control and Prevention's guidance[1]
Disease definition	PVL associated *S aureus* (*S aureus* associated with Panton Valentine leukocidin)	Community associated MRSA (meticillin resistant *S aureus*)
Role of PVL	All cases caused by PVL strains	Most cases caused by PVL strains*
Prevalence of infection	Believed to be rare	Common
Is decolonisation routinely recommended for cases?	Yes	No
Is screening recommended for contacts?	Yes, if *(a)* a contact is in a high risk group for transmission to others and decolonisation is not indicated; *(b)* there is recurrent infection in the index case after index case decolonisation	Not routinely
Is decolonisation recommended for contacts?	Yes, based on risk assessment	Not routinely
Recommendations on when to consider decolonisation of household and sexual contacts	When *(a)* the index case is infected with necrotising pneumonia; *(b)* there is a history of suspected PVL-SA skin infection in any household contact in the past year; *(c)* any high risk household contact screens positive for PVL-SA	When *(a)* multiple recurrences of MRSA infection have been documented in the index case; *(b)* ongoing MRSA transmission is documented in a defined cohort (eg, household)

*USA300 is the dominant strain of community MRSA in the United States and contains the PVL genes. In a study of skin infections in patients attending US emergency departments, 98% of MRSA infections contained the genes for PVL.[3]

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com.

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Previous articles in this series

- What is the best way to deliver subcutaneous insulin to infants, children, and young people with type 1 diabetes mellitus? (*BMJ* 2011;343:d5221)
- How big a problem is non-alcoholic fatty liver disease? (*BMJ* 2011;343:d3897)
- Do antidepressants improve negative symptoms in schizophrenia? (*BMJ* 2011;342:d3371)
- Should we treat uncomplicated symptomatic diverticular disease with fibre? (*BMJ* 2011;342:d2951)

Is ongoing research likely to provide relevant evidence?

We searched the European Clinical Trials database (EudraCT), the Clinical Trials database (Clinical Trials.gov), and the Current Controlled Trials database (ISRCTN register). Four randomised control trials in the United States are registered on the Current Controlled Trials database and will evaluate aspects of decolonisation on the incidence of PVL-SA infections in a household setting. One of these studies will evaluate decolonisation of the index case versus decolonisation of the entire household. Although these studies should answer the main research question, the results may not be generalisable to Europe because they focus on decolonisation of PVL-MRSA infections, and in Europe a substantial burden of PVL associated disease is caused by strains of meticillin sensitive *S aureus* (MSSA).[5-7]

What should we do in light of the uncertainty?

The responsibility for managing PVL-SA cases and their contacts in the community lies increasingly with primary care practitioners,[8] who may be under pressure to decolonise contacts, especially in situations where there has been a death or severe disease in the index case.

Except for necrotising pneumonia (when close contacts should be decolonised without delay), the Health Protection Agency recommends risk assessment of close contacts of PVL-SA cases to identify individuals with a history of suspected PVL-SA skin infections.[2 8] Close contacts are defined as sexual partners and anybody who has had prolonged contact with the case in the seven days before onset of illness. If there is no indication to decolonise contacts, screen the contacts if the index case has recurrent infection or if they are in a high risk group for transmission to others—for example, through occupational or recreational activities (such as healthcare workers or players of contact sports). Take specimens from the nostrils, throat, and any suspicious skin lesions, and request microscopy, culture, sensitivities, and PVL screen, stating that the individual is a contact of someone infected with PVL-SA. Follow-up screening is not recommended unless contacts are particularly vulnerable to infection, such as those having dialysis,[9] or pose a high risk of onward transmission.

If any close contact is suspected of having been infected with PVL-SA in the previous 12 months or any contact screens positive for PVL-SA, decolonisation is recommended for the entire household or family group. Treatment is for five days and comprises topical chlorhexidine 4% body wash or triclosan 1-2% once a day and mupirocin ointment applied to the nostrils three times a day. All close contacts should be treated simultaneously with the index case. Consider the severity of disease in the index case, and reinforce basic hygiene measures to reduce the spread of infection (covering of skin lesions, regular hand washing, and avoidance of sharing personal items such as towels).[2] The box outlines the Health Protection Agency's guidance on the management of contacts of individuals infected with PVL-SA infection (excluding necrotising pneumonia).

Health Protection Agency's guidance on the management of contacts of individuals infected with PVL-SA infection (excluding necrotising pneumonia)[2 8]

If any contacts may have had PVL-SA infection in the past year (such as a history of recurrent skin infection)

Decolonise all contacts in family group or household simultaneously with index case, without screening.

If any contacts are in a high risk group for transmission to others (such as healthcare workers, contact sports players, closed communities) and the criterion above is not met

Screen high risk contacts; if any of them screen positive, decolonise the whole family group or household simultaneously with the index case

If infection recurs in an index case who has been decolonised

Screen contacts; if any of them screen positive, decolonise the whole family group or household simultaneously with the index case

If contacts are not in a risk group and have no history of PVL-SA infection in the previous 12 months

Contacts do not need decolonisation or screening

RECOMMENDATION FOR FURTHER RESEARCH

Population—Index cases infected with PVL-SA and their household contacts

Intervention—Coordinated decolonisation of cases and their household contacts with intranasal mupirocin and topical chlorhexidine for five days

Control—Decolonisation of household cases; household contacts treated with placebo

Outcome—Proportion of household contacts who develop PVL associated infection after 12 months' follow-up

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EASILY MISSED?

PVL positive *Staphylococcus aureus* skin infections

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com.

Patients presenting with recurrent skin abscesses may be infected with the rapidly emerging and highly pathogenic strains of *Staphylococcus aureus* that carry the virulence factor Panton-Valentine leukocidin (PVL). PVL positive *S aureus* can be acquired in the community and lead to recurrent and potentially serious infections of the skin and necrotising pneumonia.

Why is PVL positive *S aureus* skin infection missed?

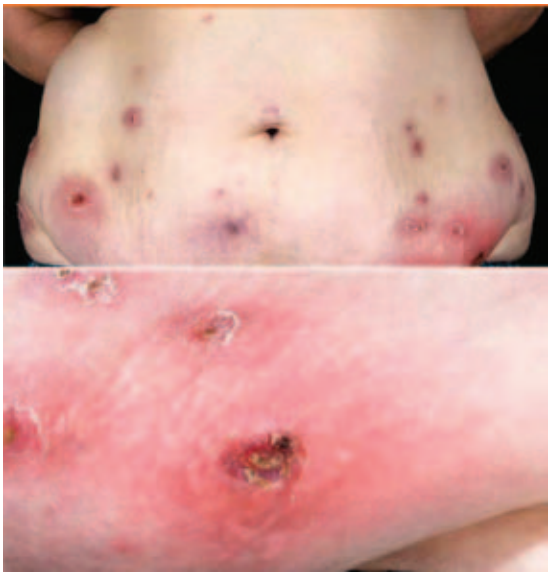
Although PVL positive *S aureus* skin infections can be suspected on clinical grounds (severity and extent of lesions, similar lesions in close contacts, frequency of relapse, and poor response to normally effective chemotherapy), it can only be confirmed by taking swabs from lesional skin, any pus, and carrier sites. The clinician must then ask the microbiology laboratory to test any *S aureus* isolates for the presence of PVL genes. PVL gene detection is not routinely tested in the UK and therefore must be specifically asked for on the request form when sending swabs. Antibiotic sensitivities alone cannot be relied on to discriminate between PVL positive and PVL negative strains of *S aureus*.

Why does it matter?

In patients with many boils or abscesses, the delayed identification of PVL positive *S aureus* can lead to serious morbidity over many months. PVL positive *S aureus* is associated with higher morbidity and mortality, and is also highly transmissible, when compared with PVL negative *S aureus*.[5] Patients may have time off work, make frequent appointments at their general practice for wound management, and take many courses of antibiotics that are clinically ineffective. The highly transmissible nature of PVL positive *S aureus* means that onward transmission is more likely with prolonged infections owing to delayed diagnosis or inadequate treatment. Rarely, PVL positive *S aureus* infections can become invasive, leading to necrotising haemorrhagic pneumonia (mortality approaching 75%[6]), necrotising fasciitis, and purpura fulminans. A quarter of patients with PVL necrotising pneumonia give a history of previous skin lesions (boils) themselves or in close family contacts.[5] From a public health perspective, early recognition and treatment of PVL positive *S aureus* infections in the UK should help to prevent the rapid rise in PVL community infections that has been seen in the United States.

CASE SCENARIO

A 39 year old woman presented with recurrent deep painful abscesses (figure) and was one of 30 similar patients referred to our dermatology unit over the past 12 months. She was otherwise well with no intercurrent illness. Routine skin swabs taken by her general practitioner grew meticillin sensitive *S aureus*, but the abscesses did not resolve after several weeks of oral flucloxacillin. Further swabs were therefore taken and the *S aureus* isolate was sent to the national staphylococcal reference unit for typing. This confirmed PVL positive *S aureus*, which is not easily eradicated from skin infections with conventional courses of flucloxacillin or erythromycin. The patient subsequently required a four week course of rifampicin and clindamycin, plus five days of chlorhexidine wash and nasal mupirocin, to clear the lesions completely. No relapse was seen six months later.



Top: Necrotising abscesses typical of PVL positive *S aureus* infection. Bottom: Cutaneous abscess with purulent discharge, central ulceration, and severe soft tissue inflammation

How is PVL positive *S aureus* skin infection diagnosed?

Clinical

Patients are usually healthy young adults.[5] Guidance from the Centers for Disease Control and Prevention refers to the "five Cs" of risk factors for PVL related infection: contaminated items; close contact; crowding; cleanliness; and cuts and compromised skin integrity.[7] In North America, settings identified as higher risk for transmission include households, close contact sports, gyms, and prisons.[5]

Patients present to their general practitioner with a history of recurrent boils or abscesses (from two to over 15 such skin lesions) over weeks or months, and other family members or contacts may be similarly affected. Our 39 year old patient (figure) presented with recurrent, deep, painful abscesses over 12 months.

Investigations

In patients with recurrent boils, necrotising skin, or soft tissue infections, when there is someone else in the household with such symptoms or if the patient is in a closed community, take a microbiology swab from infected skin and nares. Request microscopy, culture, and sensitivities, and also ask the laboratory to test for the presence of PVL positive *S aureus*.

How is PVL positive *S aureus* skin infection managed?

Most cases of PVL positive *S aureus* in the UK are currently sensitive to flucloxacillin, erythromycin, and clindamycin. The current guidelines from the Health Protection Agency recommend a seven day course of oral flucloxacillin or clindamycin for meticillin sensitive strains. They advise treat-

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- Congenital cataract (*BMJ* 2011;342:d3075)
- Giant cell arteritis (*BMJ* 2011; 342:d3019)
- Metastatic spinal cord compression (*BMJ* 2011;342:d2402)

HOW COMMON IS PVL POSITIVE *S AUREUS* SKIN INFECTION?

Recent (2010) data from the United Kingdom found that 20% of *S aureus* isolates from skin or soft tissue infections contained PVL positive *S aureus*,[1] and although the sample may have been biased towards the more severe skin or soft tissue infections, this prevalence is far higher than the 2% recorded in 2005.[2 3]

Worldwide literature reports similar figures—for example, in one study, 30% of 100 consecutive *S aureus* isolates from patients with skin or soft tissue infections that were analysed in a German university hospital laboratory were PVL positive.[4]

Currently, PVL associated with meticillin sensitive *S aureus* is less common in the UK than in the United States.[5] The prevalence in the UK of PVL positive meticillin resistant *S aureus* (MRSA) isolates from skin infections is currently estimated to be about 0.8%.[1]

Of the 30 cases of PVL positive *S aureus* causing recurrent boils seen in our unit over the past 12 months, three (10%) were PVL positive MRSA isolates.

KEY POINTS

The prevalence of PVL positive *Staphylococcus aureus* in the community is rapidly increasing

Suspect PVL positive *S aureus* infection when patients present with recurrent boils, particularly when there is a history of similar lesions in household members or close contacts

Send microbiology samples specifically requesting PVL gene detection, as well as microscopy, culture, and sensitivity

ing PVL positive meticillin resistant *S aureus* isolates with rifampicin and one other agent (clindamycin, doxycycline, sodium fusidate, or trimethoprim). In our experience in secondary care, patients that we saw with PVL positive meticillin sensitive *S aureus* infections had already failed trewatment with flucloxacillin in the community. The reasons for this are not clear; however, laboratory data relating to the management of necrotising pneumonia caused by PVL positive *S aureus* suggest that flucloxacillin may, in fact, increase PVL production.[8 9] Suboptimal tissue concentrations of flucloxacillin within necrotic lesions are also thought to be partly responsible, whereas clindamycin and rifampicin have good soft tissue penetration and work synergistically. Furthermore, to interrupt transmission of PVL positive *S aureus*, the HPA guidelines suggest that all patients plus their close contacts are treated with topical decolonisation for five days (chlorhexidine 4% wash to the body daily and mupirocin ointment applied three times daily to the anterior nares).

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ANSWERS TO ENDGAMES, p 593. For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION

Non-randomised studies

This study is best described as a before and after study (answer *c*).

ON EXAMINATION QUIZ

Fever in a returning traveller

Answer A is the correct answer.

PICTURE QUIZ Increasing confusion in a man after a fall—just a head injury?

1 **The skull radiograph shows the typical appearance of a "pepper pot" skull, characterised by numerous well defined "punched out" lytic lesions.**
2 **Multiple myeloma.**
3 **Serum electrophoresis will detect paraproteins in the blood as a band of monoclonal immunoglobulins. Urine electrophoresis will check for free light chains (Bence-Jones proteins) in the urine. Immunofixation will establish the immunoglobulin subtype in the blood and the subtype of light chain in the urine. Bone marrow aspiration and biopsy will confirm the degree of marrow infiltration and presence of malignant plasma cells by immunohistochemistry. Serum immunoglobulin concentrations are typically reduced. A radiological skeletal survey is necessary to screen for osteolytic lesions.**
4 **Initial management is with intravenous fluids (3 L/day), intravenous bisphosphonate to treat hypercalcaemia, and consideration of urgent dexamethasone to prevent further renal damage by light chains. Younger fitter patients are treated with high dose chemotherapy before stem cell transplantation. Older and less fit patients are treated with less intensive regimens, which now incorporate thalidomide to improve response. Supportive measures include treatment with analgesia and palliative radiotherapy to help improve bone pain and reduce fracture rates. Blood transfusion and erythropoietin injections are used to correct anaemia. Patients in acute renal failure may be dialysed. Acute infections are treated with appropriate antibiotics, and regular immunoglobulin infusions may be needed in recurrent infections.**