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Culture

Necrotising pneumonia due to Panton Valentine Leukocidin *Staphylococcus aureus*

Marina Morgan
Dept Medical Microbiology
Royal Devon and Exeter Hospital
Exeter, UK

Introduction

Necrotising pneumonia, with destruction of lung tissue and formation of abscesses, can be associated with Gram-negative infections, such as *Klebsiella* (aspiration pneumonia in alcoholics) or *Pseudomonas aeruginosa* (neutropenics), fungal infections (e.g. *Aspergillus* in neutropenics) or Gram-positives (Group A beta-haemolytic streptococci and *Staphylococcus aureus*). The recent increase in cases due to Panton-Valentine Leukocidin (PVL) producing *S. aureus* prompted this review, since there are implications for routine laboratories when samples are received from such patients. PVL-related disease may present in association with meticillin sensitive *S. aureus* (MSSA) and meticillin resistant *S. aureus* (MRSA). The classical presentation of PVL-associated infection is recurrent skin and soft tissue abscesses. These are the result of the compensatory, chronic over-production of polymorphs in response to the leukocidal action of the PVL toxin. Although this is the most common presentation, many hospitals are now seeing fulminating and devastating pneumonia.

PVL-associated staphylococcal pneumonia produces cavitation, lung haemorrhage (which may be massive and exsanguinating), massive tissue necrosis, abscess formation and a mortality approaching 75%[1].

PVL production is not a new phenomenon. The "Oxford staph" used as a control in laboratories is PVL positive, and PVL probably accounted for some of the mortality in the 1919 influenza epidemic[1]. "Old fashioned" PVL negative *S. aureus* pneumonia has a mortality of some 2%, whereas PVL positive *S. aureus* pneumonia has a mortality of 62-75%[1,2]. In 1919, in Fort Jackson[3], USA, when hundreds of troops were dying, clinicians commented, "the treatment of *S. aureus* infection of the lung is extremely ineffectual". Nowadays, even appropriate antibiotics have a limited capacity to alter the outcome of severe infections.

PVL was first described in 1932 by Panton (see *Figure 1*) and Valentine[4] in The London Hospital. PVL is now known to be encoded by two genes, *luk-S-PV* and *luk-F-PV*, and transferred between strains of *S. aureus* by bacteriophage. A heterogeneous mix of MSSA and MRSA strains carrying the genes for PVL production is spreading throughout Europe. Sporadic cases and small outbreaks have been reported in the UK, some spreading within hospitals, as has the emergence of new stains of PVL producing community-associated MRSA (CA-MRSA) now appearing in animals. Less than 2% of strains of *S. aureus* from invasive infections submitted to the Health Protection Agency (HPA) produced PVL[5].

A bi-component toxin, structurally similar to gamma-haemolysin, PVL comprises two sub-units (F & S) that together are leukocidal and dermonecrotic. Of *S. aureus* from invasive infections submitted to HPA, 1.6% of strains produced PVL, of which 46% were MRSA[5].

Figure 1. Dr Philip Panton

Since staphylococci spread between those living closely together with a lot of physical contact, spread of PVL-related disease is most common in families, nurseries, childcare centres, in closed establishments such as prisons, and where skin trauma encourages colonising staphylococci to adhere and then invade – e.g. turf burns, military training and athletic teams.

Community-associated or -acquired MRSA (CA-MRSA) has been defined as an isolate obtained from an out-patient (or inpatient within 48 hours of hospitalisation) in the absence of identified risk factors for acquiring MRSA. Molecularly, CA-MRSA strains contain Staphylococcal Cassette Chromosome (SCC) *mec* element types such as IV and V. Both these normally lack antibiotic resistance genes other than *mecA*, hence strains are relatively sensitive to antibiotics other than beta lactams. Most CA-MRSA carry genes encoding for PVL as well as up to 18 additional virulence factors, including toxin producing genes, (*sea, seb, sec, seh* and *sek*). CA-MRSA is characterised by enhanced spreadability, adherence to damaged skin and a propensity for necrosis, e.g. the painful necrotic lesions leading many patients in the USA to conclude, erroneously, they have been bitten by spiders.

PVL seems to enhance the spreadability of staphylococci expressing it, possibly by conferring better adherence to damaged skin. The most successful PVL-associated clones of MRSA are USA-300 & USA-400, with USA-300 more "fit" for survival. There is a clonal shift from USA-400 to USA-300 predominance, especially in correctional institutions. Finally, CA-MRSA grows faster than hospital acquired MRSA (HA-MRSA).

Professor Jerome Etienne, a world authority on PVL, estimated the incidence of PVL-associated staphylococcal pneumonia to be 1 case per 10 million persons per year, but the true incidence is unknown. A recent review of the world literature found only 141 cases[2], which must be a massive underestimate. Few cases are published, molecular testing for the PVL genes is not routine in hospital laboratories and the disease is not notifiable. In Exeter alone, since 2004, we have seen 6 cases due to unrelated strains of PVL positive MSSA, and one CA-MRSA strain.

Pathogenesis of PVL-associated staphylococcal pneumonia
Bacteria enter the lungs via the bloodstream or into the airspaces during inhalation. Post-influenza staphylococcal pneumonia is well recognised. PVL producing strains bind preferentially to basement membranes and exposed type IV collagen, colonising denuded epithelium and producing sheets of staphylococci.

Haematogenous spread from skin or soft tissue infection (SSTI), such as an infected injection site in an intravenous drug user, is a common cause of right sided endocarditis, when septic pulmonary embolisation results, shooting staphylococci into the lung vessels. There, staphylococcal multiplication and toxin production ensues in the thrombus. PVL and other toxins, particularly alpha-haemolysin, act together to produce necrosis in adjacent tissues.

The ability to colonise damaged mucosal surfaces may partly explain the rapid spread of CA-MRSA. Enhanced adherence or "stickability" has been found in a Brazilian epidemic clonal complex of MRSA associated with PVL production.

Once established, rapid bacterial multiplication produces sheets of staphylococci, and further production of other toxins ensues, particularly as the cells enter stationary phase. During the late exponential phase of growth, induction of alpha toxin expression begins, maximal production occurring during early stationary phase. Quorum sensing, whereby cell to cell communication occurs between bacteria via auto-inducer molecules, allows bacterial populations to coordinate gene expression. Induced gene expression at high cell density affects biofilm development and virulence factor expression. This mechanism may be responsible for expression of protease and alpha toxins, which are particularly cytotoxic.

PVL binding activates the approaching neutrophils, opening membrane calcium channels and liberating interleukins and other inflammatory mediators, generating a cascade of local vasodilatation, chemotaxis and additional neutrophil infiltration. Secretion of degradative enzymes and generation of superoxide ions promote necrosis. As infection spreads throughout the lung tissue, inflammatory changes result in a necrotising vasculitis with massive areas of infarction and haemorrhage.

Clinical presentation and diagnosis of PVL-associated staphylococcal pneumonia
Relatively few patients developing necrotising pneumonia have a history of skin sepsis, themselves, but often have family members or close contacts with SSTI.

The pathognomonic presentation is that of a previously fit, young patient with a recent flu-like illness, a fever of >39°C, respiratory rate >30, tachycardia of >140 beats per minute, significant haemoptysis and hypotension[1]. Marked leucopoenia and very high C-reactive protein levels (>300-400g/l) may be found, reflecting the gross tissue destruction, thrombosis and sepsis. Multilobular, alveolar infiltrates are usual, and, unlike HA-MRSA pneumonia, frequently cavitate with effusions[1,2,3].

What is presumed to have been a "viral illness" with shivers and shakes may be due to a virus or indeed secondary staphylococcal infection and bacteraemia. Together with an initially non-productive cough and normal chest X-ray, this misleading presentation leads the unfortunate clinician reviewing the patient to be falsely reassured by the lack of radiographic changes and the "normal" neutrophil count. Hence, patients may be discharged with a non-specific "viral illness" diagnosis, and often only given inhalers or ineffective low doses of oral antibiotics. Clinicians do not realise the massive white blood cell (WBC) response resulting from the staphylococcal infection has already been decimated by PVL, so what would have been a WBC count of 20-30 may instead be in the normal range. Only hours later, as necrosis and consumption of platelets and neutrophils reaches a zenith, does the classical leucopoenia occur, and now septic shock alerts the clinician to the gravity of the situation.

The rapid, extensive pneumonia evolves into an acute respiratory distress syndrome with haemoptysis, which may be massive, and, usually, a profound leucopoenia. Pulmonary manifestations associated with PVL positive MRSA may be diverse, including classical lobar pneumonia, pneumonia with pneumoatoceles, empyema, septic emboli and abscesses[3,5].

The first recognised UK case of PVL-associated pneumonia was in London in 2003, although France, America and Australia had noted cases since 1999. Not all PVL-associated pneumonia cases exhibit the classical characteristics; depending on the time since infection, patients will exhibit some or none of these symptoms, especially if the progress of infection has been affected by antibiotic therapy prior to admission.

Laboratory investigations

Leucopoenia and thrombocytopoenia are common, and a C-reactive protein, usually >300 units, would be expected. Although patients presenting in the early stages of disease may have a normal WBC count, the high C-reactive protein points to a bacterial rather than a viral infection. Haemoptysis in the setting of severe pneumonia justifies urgent Gram staining, and typically sheets of Gram-positive cocci in clusters with a paucity of neutrophils are seen (see *Figure 2*).

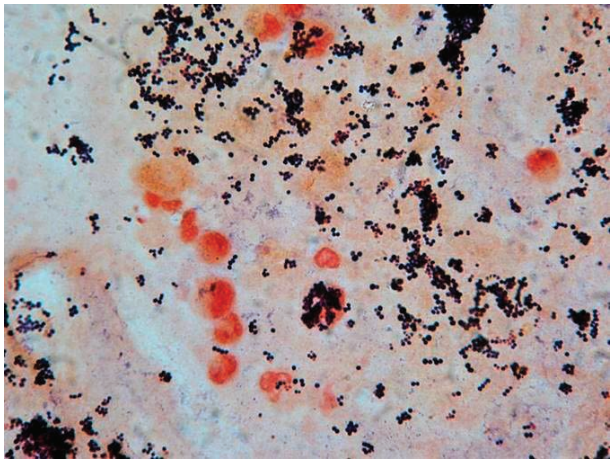

Figure 2. Gram stain of sputum from a patient admitted with PVL pneumonia. Note the paucity of leucocytes and massive numbers of staphylococci

Radiology investigation

Early on, there may be nothing to find on examination or chest X-ray. Later, the chest X-ray shows multiple areas of patchy consolidation, monolobular or multilobular infiltrates developing into cystic changes and cavitation, best visualised with a CT or MRI scan. Pleural effusions and empyema are common.

Treatment of PVL-associated staphylococcal pneumonia

For many years, GPs have known to cover for secondary staphylococcal pneumonia after influenza. Traditionally, post-viral anti-staphylococcal prophylaxis for bacterial pneumonia with co-amoxyclav, erythromycin or simply adding flucloxacillin to the local regimen for community-acquired pneumonia has sufficed – but no longer. Depressingly, even with "appropriate" initial antimicrobials, the maximal survival of PVL-associated staphylococcal pneumonia is only 38%[2].

Patients need intensive care and aggressive antibiotics. In addition to routine infection control precautions, masks should be used during intubation and physiotherapy, and closed tracheal suction should be used, since secondary cases are known to have occurred. Screening nose/throat/wounds of contacts may occasionally be necessary as secondary transmission, particularly within families and producing invasive disease, has occurred. However in Exeter, ten days following failed resuscitation of a patient with PVL MSSA pneumonia and purpura fulminans (fulminant sepsis with skin haemorrhages and gangrene reminiscent of meningococcal disease) screening swabs of all 11 healthcare workers proved negative.

With an expected mortality approaching 75%, "industrial" doses of potent, penetrating anti-staphylococcal antibiotics aimed at blocking toxin production are justifiable. Empirical therapy must cover MRSA, even in the absence of risk factors, especially with the increasing numbers of CA-MRSA in the UK.

Vancomycin, the old mainstay of MRSA therapy, is no longer appropriate particularly as monotherapy. Vancomycin does not suppress toxin formation, conventional doses produce inadequate lung concentrations, and even with high trough serum levels (15-20mg/dl) continuous breakthrough bacteraemia has been reported many days into therapy. Three of 4 patients with necrotising pneumonia failing vancomycin therapy responded to linezolid and rifampicin[6].

Which antibiotics should be used?

Even for MSSA, the bactericidal antibiotic, flucloxacillin, may not be ideal, since nafcillin increases PVL production *in vitro* at concentrations just above the MIC[7]. Nafcillin upregulates mRNA expression in both MRSA and MSSA, resulting in prolonged and increased toxin production[7]. Sub-inhibitory levels of meticillin lead to increased alpha toxin levels via increased exo-protein synthesis[8], and *in vitro*, low concentrations of oxacillin increase the concentration of PVL up to 3-fold[9].

Instead, since the necrotising process is primarily driven by toxin production, antimicrobials acting at the ribosomal level of protein synthesis seem preferable. Empirical therapy should block toxin production, penetrate dead and dying tissue, preferably be bactericidal and cover the possibility of CA-MRSA until sensitivity test results are available. Antibiotics suitable for SSTI treatment (co-trimoxazole, doxycycline) are not appropriate for fulminant pneumonia.

Unsuspected CA-MRSA infection in four Minnesotan children admitted to hospital in 1999 was the reason for failure of the empirical cephalosporin antibiotics. All four died. Predicting the sensitivity of staphylococci seen in clinical specimens is increasingly difficult, depending largely on the geographical location and clonality. Most USA-300 strains of CA-MRSA are resistant only to beta-lactams and macrolides. However, recently a strain resistant to tetracycline, fusidic acid, clindamycin and fluoroquinolones has been reported, as have strains with increasing vancomycin resistance. A PVL positive CA-MRSA strain (probably USA-300), causing necrotising pneumonia in a young Italian, had an MIC to vancomycin of 2-4. It responded to a combination of linezolid, teicoplanin and rifampicin and necessitated 6 weeks in hospital[10].

The presence of inducible clindamycin resistance shows striking differences between geographical areas. A report from Dallas showed a dramatic fall in resistance over 3 years, associated with a clonal shift. Laboratories should routinely "D test" all *S. aureus* isolates appearing to be erythromycin resistant and clindamycin sensitive to exclude inducible clindamycin resistance. Clindamycin resistance is particularly prevalent in CA-MRSA strains in Taiwan.

Proteomic studies showed that linezolid, one of a new class of antimicrobials, the oxazolidinones, reduced the tumour necrotising factor (TNF) inducing activity of *S. aureus* in a dose dependent manner, reduced expression of virulence factors alpha and beta haemolysins, and decreased protein A[11]. Clindamycin suppresses protein synthesis, including alpha and delta haemolysin, coagulase production *in vitro* and exo-protein expression, including alpha toxin.

The combination of clindamycin and linezolid has proven synergistic *in vitro* and is our recommended initial therapy pending antibiotic sensitivity results. Combinations of anti-staphylococcal antimicrobials, such as rifampicin, flucloxacillin and cephalosporins, have also been used with varying degrees of success[2]. In Exeter, we use 1.2-1.8 grams intravenous clindamycin, 6-hourly, and linezolid 600mg, 12-hourly. Latterly, addition of a third antibiotic, rifampicin, coincided with significant improvement, and so now we would use all three initially, since the rifampicin is active against intracellular staphylococci.

Of the quinolones, *in vitro* studies show that moxifloxacin is far superior to ciprofloxacin in treating CA-MRSA strains, and of the newer antimicrobials, daptomycin, being inactivated in surfactant, is not recommended.

Therapy should be continued until clinical signs improve and markers of infection have stabilised. A minimum of 2-3 weeks seems reasonable especially if vancomycin is being used, as many patients may have been bacteraemic, and PVL-associated disease has a high incidence of sequelae and metastatic foci, (pleural effusions, infected thrombi, etc) particularly in children.

Adjunctive therapy for PVL-associated infections

Intravenous immunoglobulin (IVIG)

We routinely add intravenous immunoglobulin, 2g/kg, for its beneficial immunomodulatory action for patients in toxic shock, as it neutralises superantigens and circulating toxins. This is repeated at 48 hours if there is still evidence of sepsis or failure to respond. IVIG neutralises PVL pore formation and the cytopathic effect of PVL *in vitro*, inhibition being concentration dependent[12].

Protein C

Whilst anecdotal reports suggest a possible role for activated Protein C, it is contraindicated in active bleeding, which may be occurring before frank haemoptysis develops.

Extra-corporeal membrane oxygenation (ECMO)

This process, where the lungs are bypassed and the blood is oxygenated outside the body, is available in only one or two centres in the UK. ECMO has been used in Sweden, the USA and, recently, in the UK for PVL pneumonia, although with few successes to date.

Future therapies

Inactivation of toxins that have already been produced and continue to drive the necrosis may be the key to improving survival. Potential areas for research include nebulised immunoglobulin, which we have used successfully, glycerol monolaurate, staphylococcal vaccination, and perhaps re-visiting old treatments such as leukocidin toxoid and phage therapy.

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Erysipelothrix rhusiopathiae: forgotten but not gone

Qinning Wang and Thomas V Riley
Microbiology & Immunology
The University of Western Australia
and Division of Microbiology & Infectious Diseases
Queen Elizabeth II Medical Centre
Nedlands, Western Australia

Erysipelothrix rhusiopathiae infection

Erysipelothrix rhusiopathiae is a facultative, non-spore forming, non-acid fast, small, Gram-positive bacillus. The name means literally 'erysipelas thread of red disease'. The organism has had a long history and many nomenclature changes. The earliest member of the genus *Erysipelothrix* was termed *Erysipelothrix muriseptica* when first isolated by Koch in 1876 from the blood of mice with septicaemia. In 1882, a bacillus was observed, in pigs dying of infection, by Pasteur and Dumas. Later, Loeffler reported a similar bacillus in the skin blood vessels of a pig that had died of swine erysipelas. This was the first description of this organism as an infectious agent causing disease in swine[1].

E. rhusiopathiae was first described as a cause of human disease in 1870, and further cases were documented in 1873 as erythema serpens. *Erysipelothrix* was not established as a human pathogen until 1884, when Rosenbach isolated an organism from a patient with localised cutaneous lesions. He used the term 'erysipeloid' to differentiate between the human streptococcal disease, erysipelas, and the condition he had observed[1]. Subsequently, *Erysipelothrix* has been identified as the cause of infection in many animal species. Rosenbach distinguished three separate species of the organism, *E. muriseptica, E. porci* and *E. erysipeloid*, based on their isolation from mice, pigs and humans, respectively. It was realised later that these three organisms were nearly identical strains of the same species. The name *E. insidiosa* was proposed for them originally by Trevisan in 1885. This and all 36 other documented names for the organism were rejected in 1966 in favour of *E. rhusiopathiae*, a combination that originated in 1918.

Three forms of human disease have been recognised, including a localised cutaneous lesion form, erysipeloid, which was so-called to distinguish it from the human streptococcal disease erysipelas, a generalised cutaneous form and a septicaemic form often associated with endocarditis[2]. *E. rhusiopathiae* is ubiquitous and able to persist for a long period of time in the environment, including marine locations. It is a pathogen or a commensal in a wide variety of wild and domestic animals, birds and fish. Swine erysipelas is the disease of greatest prevalence and economic importance. Diseases in other animals include erysipelas of farmed turkeys, chickens, ducks and emus, and polyarthritis in sheep and lambs. The organism causes no known disease in fish but can survive for long periods of time on the mucoid exterior slime of fish[3].

Infection due to *E. rhusiopathiae* in humans is occupationally related, principally occurring as a result of contact with contaminated animals, their products or waste, or soil. Erysipeloid is the most common form of infections in humans. Some other names have been used to describe this infection, including whale finger, seal finger, speck finger, blubber finger, fish poisoning, fish handler's disease, and pork finger[4]. These reflect the occupational attributes of the disease. While it has been suggested that the incidence of human infection could be declining due to technological advances in animal industries, infection still occurs in specific environments. Additionally, infection by the organism is possibly under-diagnosed due to the resemblance of *Erysipelothrix* infections to other infections, and problems encountered in isolation and identification. Diagnosis of erysipeloid can be difficult if not recognised clinically, as culture is lengthy and the organism resides deep in the skin.

E. tonsillarum and other unnamed species were classified in the genus of *Erysipelothrix* 20 years ago[5]. *E. tonsillarum* was considered morphologically and biochemically identical to *E. rhusiopathiae*. However, *E. tonsillarum* could ferment sucrose while *E. rhusiopathiae* could not[6]. The pathogenicity of other *Erysipelothrix* species is not well understood. *E. tonsillarum* is frequently isolated from tonsils of healthy pigs, cattle and broiler chickens. It was reported that *E. tonsillarum* was avirulent for swine and mice[5]. However, some studies have identified *E. tonsillarum* as a cause of endocarditis in dogs, indicating that some strains of *E. tonsillarum* may be canine pathogens[7].

Various virulence factors may be involved in the pathogenicity of *E. rhusiopathiae*. The presence of a hyaluronidase and neuraminidase has been recognised, and neuraminidase plays a significant role in bacterial attachment and subsequent invasion into host cells. The role of hyaluronidase in the disease process is controversial, however, the capsule is an important virulence factor[8].

Isolation and identification of *E. rhusiopathiae*

E. rhusiopathiae is most likely to be confused with other Gram-positive, non-sporing, rod shaped bacteria, such as members of the genera *Brochothrix, Corynebacterium, Lactobacillus, Listeria, Kurthia* and *Streptococcus*. Identification of *Erysipelothrix* species is based on Gram stain (see *Figure 1*), cultural morphology, motility, haemolytic characteristics and biochemical properties, particularly hydrogen sulphide production[4]. Sucrose fermentation can differentiate *E. rhusiopathiae* from *E. tonsillarum*. *E. rhusiopathiae* can be distinguished from other Gram-positive bacteria by the following: non-motility; absence of β-haemolysis; inhibition of growth by

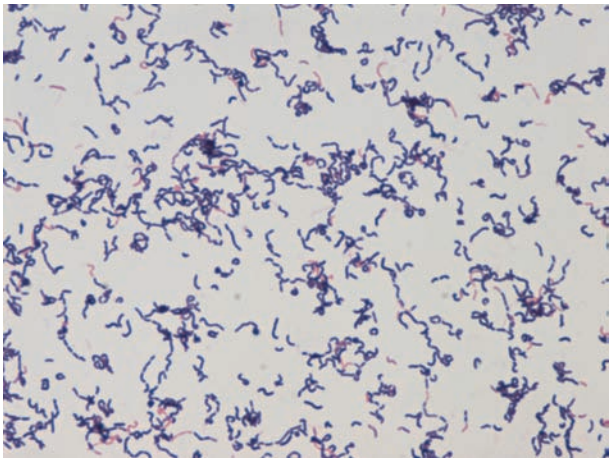

Figure 1. Gram stain image of a smooth colony of *Erysipelothrix rhusiopathiae*

potassium tellurite; inability to ferment salicin and trehalose or to produce catalase; weak, red coloured formazan production from 2, 3, 5,-triphenyltetrazolium chloride; extracellular site of infection; poor pathogenicity for guinea pigs; absence of keratitis after inoculation of rabbit conjunctival sac; serologic typing; and resistance to neomycin. *Table 1* shows some differential features of *Corynebacterium, Listeria* and *Erysipelothrix*.

Table 1. Differential features of *Corynebacterium, Listeria* and *Erysipelothrix*[13]

Characteristic	*Corynebacterium*	*L. monocytogenes*	*E. rhusiopathiae*
Bacteriology			
Motility	usually -	+	-
Haemolysis	variable	Beta	Alpha
Growth in potassium tellurite	+	+	-
Biochemical			
Salicin fermentation	+/-	+ (acid)	-
Trehalose fermentation	+/-	+ (acid)	-
Catalase	usually +	+	-
Pathology	extracellular	intracellular	extracellular
Animal inoculation			
Mouse infection	not susceptible	susceptible	susceptible
Guinea pig infection	not susceptible	susceptible	not susceptible
Conjunctival sac of a rabbit	no effect	severe kerato-conjunctivitis	mild conjunctivitis; no keratitis
Serology	-	4 serotypes(1-4)	3 serotypes (A, B, & N)
Neomycin susceptibility	variable	susceptible	resistant

E. rhusiopathiae colonies are described as clear, circular and very small, with a diameter of 0.1-0.5mm after 24h incubation at 37°C, or 0.5-1.5mm after 48h. Two distinct morphological forms grow on solid agar media. Smooth (S) colonies are bluish, transparent and convex. Microscopically, these appear as small, slightly curved, slender rods with rounded ends, about 0.8-2.0µm long and 0.2-0.4µm wide. Rough (R) colonies are larger and have a flat rough surface with irregular edges. Long filaments up to 60µm or more, in chains, can be seen under the microscope (see *Figure 2*). Morphology may change with alterations in pH and incubation temperature. A pH of 7.6-8.2 favours the S-form while the R-form predominates at pH <7.0. The S-form grows better at 33°C and the R-form favours 37°C[9]. The role played in disease by different colonial forms has not been determined. Most strains exhibit a narrow zone of α-haemolysis on blood agar, and β-haemolysis is never observed[9, 10].

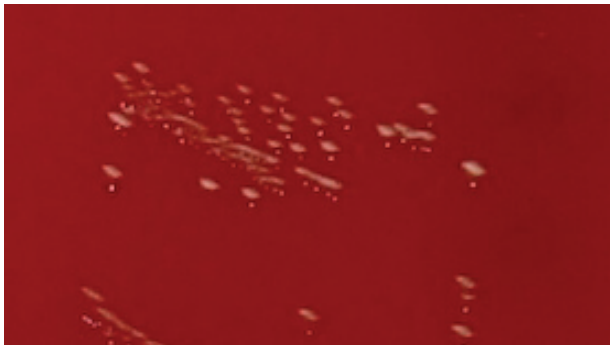

Figure 2. Plate culture showing both smooth and rough colonies of *Erysipelothrix rhusiopathiae*

Traditionally, culture methods for the isolation of *E. rhusiopathiae* involve the use of selective and enrichment media. Commercially available blood culture media are satisfactory for primary isolation from blood since *E. rhusiopathiae* is not particularly fastidious. All selective media make use of the resistance of *E. rhusiopathiae* to antibiotics and tolerance of chemicals. Each has good aspects, but none is ideal. More recently, molecular methods for detection of *Erysipelothrix* have been developed[11] and combination enrichment-PCR methods described[12].

Epidemiology of *Erysipelothrix* infection

E. rhusiopathiae is ubiquitous in nature, being found wherever nitrogenous substances decompose. *E. rhusiopathiae* and infections caused by this organism are worldwide in distribution and affect a wide variety of vertebrate and invertebrate species[1,13,14]. Human disease can originate from an animal or environmental source.

Swine erysipelas caused by *E. rhusiopathiae* is the disease of greatest prevalence and economic importance. It is economically detrimental to the pig industries of North America, Europe, Asia and Australia[3]. Polyarthritis of sheep and lambs and erysipelas in calves, ducks and domestic turkeys are also economically significant diseases caused by *E. rhusiopathiae*[1]. In Australia, *E. rhusiopathiae* causes polyarthritis in pigs, and it is an emerging problem in farmed emus.

The domestic pig is the most important reservoir of *E. rhusiopathiae*. It is estimated that 30-50% of healthy swine harbour the organism in their tonsils and other lymphoid tissues. Carriers can discharge the organism in their faeces, urine, saliva and nasal secretions, creating an important source of infection. Soil, bedding, food and water can be contaminated by infected pigs, leading to the indirect transmission of the organism. Over 30 species of wild birds and at least 50 species of wild mammals[3] are known to harbour *E. rhusiopathiae*, providing an extensive reservoir.

The organism can survive for long periods in marine environments. The slime on fish appears to be an important source of infection for man. The organism has been isolated from the environment, but this may be secondary in importance to animal reservoirs as a source of *E. rhusiopathiae*. Although *E. rhusiopathiae* is killed by moist heat at 55°C for 15 min, it is resistant to many food preservation methods, such as salting, pickling and smoking[10].

E. rhusiopathiae infection in humans is occupationally related. It occurs mostly in those people whose jobs are closely related with contaminated animals, their products or wastes, or soil. People with the highest risk of exposure include butchers, abattoir workers, veterinarians, farmers, fishermen, fishmongers and housewives[14]. The infection has also been associated with a wide variety of occupations, including meat cutters, meat-processing workers,

Table 2. Distribution of MICs for 63 *E. rhusiopathiae* strains[16]

Antimicrobial agent	No. of strains with the following MIC (µg/ml)													
	0.03	0.05	0.1	0.2	0.39	0.78	1.56	3.13	6.25	12.5	25	50	100	>100
Penicillin G	8	28	27											
Ampicillin	11	23	29											
Erythromycin		11	26	26										
Oleandomycin				1	4	38	20							
Oxytetracycline								38	2	21	2			
Chloramphenicol							1	4	13	44	1			
Dihydrostreptomycin							3	4	8	32	1	3	7	5
Kanamycin														63
Sulfadimethoxine														63

poultry-processing workers, meat inspectors, rendering-plant workers, knackers, animal caretakers, bone button makers, game handlers, furriers, leather workers, soap makers, fertiliser workers, sewer workers, bacteriology laboratory workers and stockyard workers[1]. The common names for human infection reflect this occupational mode of acquisition. Most cases in humans and other animals may occur via scratches or puncture wounds of the skin[1]. In some cases it appears that the organism has penetrated intact skin. Human-to-human infection has not been documented.

Although infection is usually self-limiting, relapses and progression to more serious forms are possible. The generalised cutaneous form of the disease caused by *E. rhusiopathiae* involves lesions that progress from the initial site to other locations on the body or appear at remote areas. The lesions are similar to those of the localised form, but bullous lesions can also occur. Systemic symptoms such as fever and joint pains are more frequent than in the localised form. The clinical course is more protracted and recurrences are common.

Septicaemia is a more serious manifestation of *E. rhusiopathiae* infection, almost always linked to endocarditis. It rarely develops from localised infection. Fifty cases with systemic infection in 15 years were reported with an extremely high incidence (90%) of endocarditis[4]. A high male-to-female ratio among patients with *E. rhusiopathiae* endocarditis was observed[2], which may reflect occupational exposure, and a greater propensity for involvement of the aortic valves. The mortality was 38%, almost double the rate for endocarditis with other bacteria. Nearly 60% of patients had normal heart valves before they were affected. Congestive heart failure, present in 80% of patients, was the most common complication of endocarditis. Diffuse glomerular nephritis and meningitis have also been reported as complications. Alcohol abuse and loss of immuno-competence were believed to be the risk factors.

Treatment and prevention of *Erysipelothrix* infection

Although antibiotic susceptibility data for *Erysipelothrix* are still limited, erysipeloid can be effectively treated with oral penicillin[4]. *Table 2* shows the distribution of MICs for 63 *E. rhusiopathiae* strains reported by Takahashi *et al.*[16]. A more recent study showed that penicillin and ceftriaxone, with low minimum inhibitory concentrations of 0.03mg/l and 0.125mg/l, respectively, remained active against *E. rhusiopathiae*, and it was suggested that they should continue to be recommended for treatment[15].

Oral penicillin will resolve a case of erysipeloid in around 48h, but intravenous penicillin is recommended for more serious *E. rhusiopathiae* infections[13]. Although the mortality rate for endocarditis has been reduced from the 100% seen in the pre-antibiotic era, it is still 38% for *Erysipelothrix* endocarditis in spite of available treatment[2]. This rate may partly be explained by the use of vancomycin (to which the organism is resistant) in the empirical therapy of endocarditis. No recent data are available on mortality in humans. Early diagnosis of all forms of *E. rhusiopathiae* infection is therefore essential. In those allergic to penicillin, cephalosporins have been described as the most appropriate alternative, since clindamycin and erythromycin are only bacteriostatic for *E. rhusiopathiae*[4].

Containment and control of *E. rhusiopathiae* are effective in preventing the spread of infection in humans and animals. For individuals working in at-risk occupations, an awareness of the infection is essential. Suggested preventative measures include the wearing of gloves or other protective handwear, good hygiene, especially frequent hand washing with disinfectant soap and the prompt treatment of any small injuries[1]. Good health is considered to be an important factor in prevention since poor health, including alcoholism, may predispose to more serious forms of infection[2].

The removal or regular disinfecting of contaminated sources is an important method of limiting the spread of the organism throughout a work environment[1]. *E. rhusiopathiae* can be killed by commonly available disinfectants. A recent study found that several commercially available home disinfectants were effective in killing *E. rhusiopathiae*[15]. Many investigators have noted, however, that structurally complex equipment is difficult to clean and, because the organism is able to survive in organic matter, disinfecting without cleaning is useless. If disinfection is impractical, other control measures become more important. Control of reservoir populations of *E. rhusiopathiae* is impractical or impossible because of the widespread distribution of the organism, the large variety of animal hosts and its ability to persist in the environment.

Control of animal disease by sound husbandry, herd management, good sanitation and immunisation procedures is recommended[3]. *Erysipelothrix* infection causes substantial economic losses in animal industries. Appropriate prophylactic measures are taken for the treatment and control of this disease. Antibiotic therapy is effective, and penicillin is usually the drug of choice. Vaccination is considered a useful procedure for controlling the problem in animal farms. Most commercially available vaccines are attenuated, live *E. rhusiopathiae* strains or bacterins[3]. These vaccines offered protection to pigs and turkeys. The duration of immunity of these vaccines varies between 6 and 12 months, and the efficacy is variable, depending on the strains used and use of the appropriate vaccine in different species of animals. Vaccination of humans is not considered to be a viable option because clinical erysipeloid appears to convey little or no immunity as shown by relapse of infection.

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Eric Bridson Bows Out

Dr Eric Bridson has stepped down from the Editorial Board of Culture after 27 years service.

At the time of the inception of Culture in 1978, Eric was Technical Director of Oxoid Limited, part of the Brooke Bond Group. The publication was the brainchild of Eric and George Fleming (then Marketing Director of Oxoid Ltd), conceived as a way for Oxoid to provide a service to microbiology by publishing articles covering a wide and eclectic range of topics from within the field of microbiology. Topics covered have been as diverse as from *Antarctic micro-organisms: coming in from the cold* to *Mycobacteria and HIV – a deadly combination* from *Emporiatrics and Jet Flight* to *The role of microbial slimes in biodeterioration.*

Eric retired from the Oxoid Board of Directors in 1988 but maintained his position on the Culture Editorial Board until November 2007, when he finally decided to step down. A presentation was made to mark the occasion.

The Culture Editorial Board and all of us at Oxoid would like to express our most sincere gratitude for all that Eric has contributed to both Oxoid and Culture. We send him our very best wishes for the future.

Ali Ball
Vice President, Marketing & New Product Development

Published by Oxoid as a service to Microbiology.
Our thanks go to the Culture editorial board: Professor Grahame W Gould, Dr David Petts, Mr David E Post and Dr Peter Stephens.

OXOID
DEDICATED TO MICROBIOLOGY

Oxoid, Wade Road, Basingstoke, Hants, RG24 8PW UK.

Tel: +44 (0) 1256 841144
Fax: +44 (0) 1256 329728
Email: oxoid@thermofisher.com

wwww.oxoid.com
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