Bacterial Diseases

Linda Jean Vogelnest

Abstract

Accurate diagnosis of feline bacterial skin diseases is important for both patient well-being and appropriate use of antibiotics in times of increasing antimicrobial resistance. This chapter reviews knowledge of clinical lesions and historical features associated with feline bacterial infections, skin diagnostics relevant to efficient and accurate diagnosis, and current treatment recommendations. Deep infections including nocardiosis and mycobacteriosis (Chapter, Mycobacterial Diseases) are well-reported, and although accurate diagnosis is important, and treatment may be lengthy and challenging, they do occur only rarely. In contrast, superficial bacterial pyoderma (SBP) is a more common feline presentation that may be under-recognised, most typically complicating underlying allergic skin disease, but also associated with a range of underlying diseases and factors. SBP is reviewed in this chapter, along with deeper infections including deep bacterial pyoderma, cellulitis and wound abscessation, dermatophilosis, necrotizing fasciitis and environmental saprophytic bacterial infections including nocardiosis. Confirmation of bacterial skin disease in cats is readily achievable in a general practice setting. Cytology is often the most valuable tool, used in conjunction with clues from the history and physical examination and supplemented with skin surface or tissue culture and/or histopathology when indicated. Cytology methods relevant to bacterial infections in the cat are detailed in this chapter. Treatment principles are also discussed, including the potential role of methicillin-resistant staphylococci in feline pyoderma, with a focus on current worldwide recommendations that may supersede some outdated clinic protocols.

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Introduction

Bacterial dermatoses in the cat occur in two broad presentations reflecting the depth of skin invasion. Superficial infections, involving the epidermis and follicular epithelium, are most common and primarily associated with multiplication of resident skin microbiota secondary to reduced local and/or systemic host defences. Deep bacterial infections, involving the dermis and/or subcutaneous tissues, may be extensions of superficial infection or associated with traumatic implantation of a range of environmental or commensal bacterial species. Some rare but life-threatening deep bacterial infections have a propensity for body dissemination.

Normal Feline Cutaneous and Mucosal Bacterial Microbiota

There is limited knowledge about normal commensal bacteria in cats, with most studies culture-based and focused on staphylococcal isolates. The mouth, followed by the perineum, appears to be the most consistent staphylococcal carriage site [1]. Fifteen species of staphylococci were identified by MALDI-TOF testing of isolates from the oropharynx of healthy cats in Brazil, with *S. aureus* the only coagulase-positive staphylococcus (CoPS) species, with a range of coagulase-negative staphylococci (CoNS) [2]. However, α-haemolytic streptococci were more frequently isolated than staphylococci from healthy mouths of free-roaming cats in Spain, followed by two Proteobacteria (*Neisseria* spp. and *Pasteurella* spp.) [3].

Staphylococci have also been less frequently identified as resident skin bacteria in normal cats, with *Micrococcus* spp., *Acinetobacter* spp. and *Streptococcus* spp. most common [4]. Of staphylococci isolated, CoNS including *S. felis*, *S. xylosus* and *S. simulans* have been more frequent than CoPS [4–6], with *S. felis* potentially misidentified as *S. simulans* in some studies [5, 7]. Either *S. intermedius* (reclassified as *S. pseudintermedius* in 2005) [1, 8] or *S. aureus* [5, 9, 10] are variably reported as the more frequent CoPS isolates. *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas* spp., *Alcaligenes* spp. and *Bacillus* spp. are less frequent isolates from normal feline skin [4, 5].

More recent genomic DNA studies in healthy cats ($n = 11$) identified a greater diversity and number of bacteria on normal feline skin than culture-based studies. Haired skin had the greatest diversity of species, the pre-aural space the greatest richness and evenness of species, and mucosal surfaces (nostril, conjunctiva, reproductive) and the ear canal (contrasting to dogs) the lowest species diversity. As for culture-based studies, *Staphylococcus* spp. did not dominate, with Proteobacteria (*Pasteurellaceae*, *Pseudomonadaceae*, *Moraxellaceae* [e.g. *Acinetobacter* spp.]) most frequent, followed by Bacteroides (*Porphyromonadaceae*), Firmicutes (*Alicyclobacillaceae*, *Staphylococcaceae*, *Streptococcaceae*), Actinobacteria (*Corynebacteriaceae*, *Micrococcus* spp.) and Fusobacteria. It is acknowledged that some species including *Propionibacterium* spp. may have been under-recognised in this study [11].

Bacterial residents vary between individuals [4, 11] and may also vary between healthy and diseased states. Carriage of staphylococci is known to increase in humans and dogs with atopic dermatitis. Similarly, *Staphylococcus* spp. were more frequently detected in allergic cats ($n = 10$) compared to normal healthy cats, with more dominance at some anatomic sites (e.g. ear canal) [11]. *Staphylococcus* spp. were also more prevalent in diseased mouths compared to normal mouths [3]. In contrast, there was no statistical difference in isolation of *Staphylococcus* spp. in another study ($n = 98$) from healthy skin compared to inflamed skin [9].

In summary, the feline studies to date suggest, in contrast to dogs, that Proteobacteria including *Acinetobacter* spp., *Pasteurella* spp. and *Pseudomonas* spp. are more common on normal feline skin than *Staphylococcus* spp., and amongst staphylococci, that CoNS appear to dominate. It is uncertain if staphylococci in general, and CoPS or CoNS in particular, multiply more readily on diseased skin.

Superficial Bacterial Pyoderma

Feline superficial bacterial pyoderma (SBP) is increasingly recognised and reported in 10–20% of cats presenting to dermatology referral [12–14]. As in other species, SBP in cats is a secondary disease, most commonly reported with hypersensitivities [12–14]; 10% of cats presenting to referral in the USA [14] and 60% in Australia had confirmed underlying allergy, most commonly atopic dermatitis [13]. Recurrent pyoderma is also commonly reported [13, 15].

Bacterial Species

Although *Staphylococcus* spp. are considered the likely pathogens [1, 2, 9, 12], weaker adherence of *S. pseudintermedius* and *S. aureus* to normal feline corneocytes in contrast to canine and human corneocytes has been documented [16], and the casual bacterial species in feline SBP have only been confirmed in a small number of cats. *S. aureus* was isolated in pure culture from papules and crusts of one cat, with concurrent neutrophils on skin cytology, and complete resolution of lesions by 10 days of antibiotic therapy [17]. *S. felis* was isolated from the nostrils and skin lesions (excoriations) of another cat with suspected underlying flea bite hypersensitivity, with concurrent neutrophils and intracellular cocci on cytology, and complete resolution of lesions by 14 days of antibiotic therapy and flea control [5]. Eosinophilic granuloma complex lesions may also be complicated by secondary pyoderma, and the most common isolates from surface swabs and/or tissue biopsies from eosinophilic plaques or lip ulcers ($n = 9$), with concurrent neutrophils and intracellular cocci on cytology, were *S. pseudintermedius* and *S. aureus*. Other isolates detected in this study included CoNS, *Pasteurella multocida*, *Streptococcus canis* and *Pseudomonas aeruginosa* [12].

A number of other bacterial culture studies, predominantly on laboratory isolates from a range of skin lesions unconfirmed as pyoderma, have focused on staphylococci; whether isolates were pathogenic or incidental is uncertain, and non-staphylococcal isolates are rarely reported [4, 7, 9, 17–19]. CoNS are the most common isolates in a number of studies, accounting for 96% of isolates from 'inflamed skin' (n = 24) [9], the second most frequent isolate (*S. simulans*) from abscesses, miliary dermatitis, excoriations, exfoliative dermatitis or eosinophilic plaques (n = 45) [17] and the most frequent isolates (*S. felis* followed by *S. epidermidis*) from unspecified 'dermatitis' [7]. Less common CoNS isolates include *S. hyicus*, S. *xylosus* and *S. schleiferi* subsp. *schleiferi* [9, 17].

CoPS have been more prevalent in some studies on diseased feline skin [4], with *S. aureus* (n = 69) [9, 17] or *S. intermedius* (n = 9 [5]; n = 30 [20]) the most frequent isolates, and *Streptococcus* spp. (10%), *Proteus* spp. (10%), *Pasteurella* spp. and *Bacillus* spp. (10%) also reported [20].

The relative importance of staphylococci in general, and CoNS and CoPS in particular, to feline pyoderma and whether there is one predominant causal species as for bacterial pyoderma in humans (*S. aureus*) and dogs (*S. pseudintermedius*) is currently uncertain.

Clinical Presentation

A median age of onset of 2 years is documented for feline SBP, although a wide range is reported (6 months to 16.5 years), with older cats also frequently affected (first presentation at >9 years of age in 23% of cats) [13]. Pruritus is common, particularly with underlying hypersensitivity, reported in 92% of cats with SBP in Australia and often severe (56%) [13]. Lesions associated with feline SBP often reflect self-trauma, consisting most typically of multifocal, crusted, alopecic, excoriated and erosive to ulcerative lesions (Figs. 1, 2, 3 and 4). Eroded papules, eosinophilic plaques, eosinophilic granulomas and rare pustules are also reported. The most frequent lesional sites are the face, neck, limbs and ventral abdomen [12, 13, 21].

Diagnosis

Although some clinical lesions have been recognised as useful diagnostic clues for bacterial pyoderma in dogs [22, 23], SBP lesions in cats are less characteristic, with many non-specific presentations (e.g. erosions, crusting). Diagnostic tests are thus important to confirm a diagnosis of feline pyoderma (see later section on "Cytology", Table 1) and are strongly encouraged prior to consideration of treatment with systemic antimicrobials [22–24].

Cytology has been considered the most useful single test, with the presence of neutrophils and intracellular or associated bacteria being diagnostic (Fig. 11a)

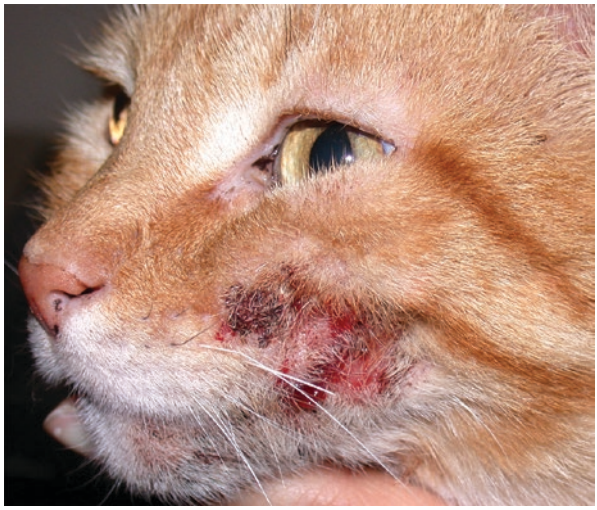

Fig. 1 Feline secondary bacterial pyoderma (SBP): exudative erosions and crusting

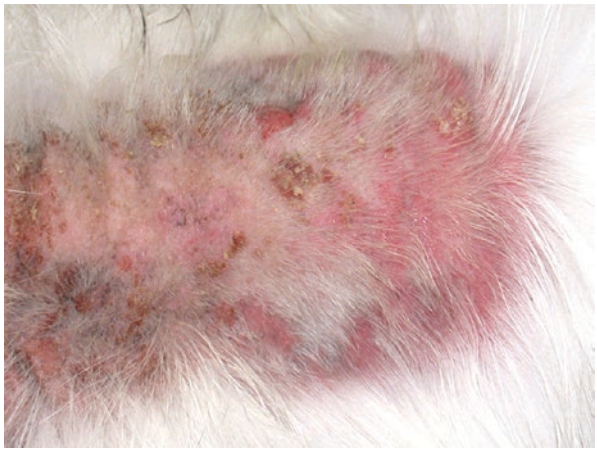

Fig. 2 Feline SBP: alopecia, erythema and focal crusting

[12, 13, 22, 25]. In canine pyoderma, cytology is considered mandatory when typical lesions (pustules) are not present or scant and is also essential to identify concurrent or alternate *Malassezia* dermatitis [23]. The morphology of bacteria on cytology (cocci and/or rods) will also guide valid empirical treatment choices and/or the need for bacterial culture. Adhesive tape impressions are applicable to all superficial skin lesions, in particular dry lesions and restricted body sites, while glass slide impressions are suitable for erosive to ulcerative lesions [22]. In canine SBP, it is reported that inflammatory cells and bacteria may be absent or scarce with concurrent immunosuppression from disease or drugs [23].

Histopathology is infrequently discussed in relation to diagnosis of SBP; however, it can provide further diagnostic confirmation, especially if samples are

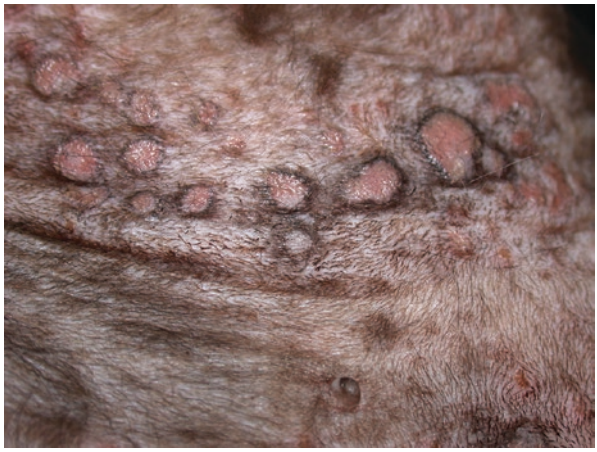

Fig. 3 Feline SBP: erythematous eroded plaques

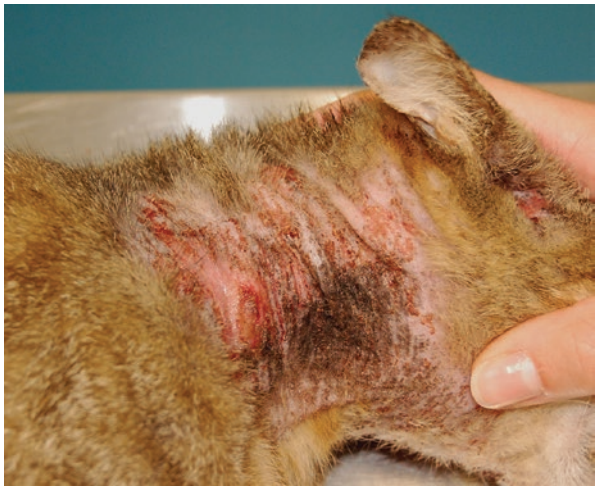

Fig. 4 Feline SBP: well-demarcated alopecia and erythema with focal crusting

collected without prior skin surface cleansing or disinfection as bacterial colonies are frequently observed within the crusts (Fig. 5) (see later section on Histopathology). Histopathology is also valuable to aid exclusion of other differentials for atypical presentations or when a diagnosis is uncertain [22].

Bacterial culture is not helpful for diagnosis of SBP, particularly when assessed independently of cytology, as isolation may simply reflect normal commensal species not involved in disease (see later section on Bacterial Culture) [6]. A heavy pure culture of one bacterial species is more likely associated with a pathogen than mixed-species isolation, but concurrent cytology remains essential [1]. Coagulase status of any staphylococci isolated is less helpful for feline pyoderma, as both CoNS and CoPS are potentially pathogenic. Despite a limited role diagnostically, culture and antibiotic susceptibility testing (C&S) can be important to guide appropriate antibiotic therapy, particularly when antimicrobial resistance is more likely.

Table 1 Differential diagnoses and valuable diagnostic tools for cutaneous lesions associated with bacterial infections in cats

Lesion	Common differentials	Less common differentials for lesion	Diagnostic tools
Papules	SBP, allergy[a] dermatophytosis	Ectoparasites (*Otodectes*, larval ticks, trombiculids); pemphigus foliaceus	History (parasiticides, exposure/contagion), cytology (tape impression), biopsy (histo)
Alopecia, erythema, scaling, crusting	SBP, dermatophytosis, allergy[a], actinic keratoses (non-pigmented skin)	Demodicosis (*D. gatoi*, *D. cati*), pemphigus foliaceus, ectoparasites (*Cheyletiella*, lice)	History (potential exposure/contagion, pruritus or lesions first), cytology (tape impression), biopsy (histo)
Erosion, ulceration, crusting	SBP, allergy[a], SCC (non-pigmented skin)	Herpes viral dermatitis, SCC in situ, cutaneous vasculitis	History (degree of pruritus, recurrent/seasonal), cytology (tape or slide impression), biopsy (histo)
Erythematous plaques	SBP, allergy[a]	Cutaneous xanthoma	Cytology (tape or slide impression), biopsy (histo)
Nodules (lip, chin, linear)	SBP, DBP, allergy[a]	Mycetoma, neoplasia (SCC)	Cytology (FNA), biopsy (histo)
Nodules (poorly demarcated)	Bacterial cellulitis/abscessation	Mycobacteria, *Nocardia*, sterile panniculitis	Cytology (FNA), biopsy (histo, C&S)
Nodules (discrete)	Neoplasia (variety), eosinophilic granuloma	Pseudomycetoma (bacterial, dermatophyte), mycetoma, histiocytosis, sterile pyogranuloma	Cytology (FNA), biopsy (histo, C&S)
Pustules (rare)	SBP, pemphigus foliaceus	Dermatophytosis	Cytology (impression after rupture), biopsy (histo)

[a]Atopic dermatitis, adverse food reactions and/or flea bite hypersensitivity
C&S culture and antibiotic susceptibility testing, *DBP* deep bacterial pyoderma, *FNA* fine needle aspirates, *histo* histopathology, *SBP* superficial bacterial pyoderma, *SCC* squamous cell carcinoma

Treatment

There are limited studies evaluating treatment of feline SBP, and most recommendations are anecdotal. However, recent guidelines stress the importance of confirming a diagnosis of SBP prior to considering systemic antibacterial therapy (see later section on Antibiotic Stewardship (Box 1)) [1, 22, 23]. Over-utilisation of antibiotics without confirmation of diagnosis is well-recognised, and the common practice of prescribing antibiotics 'just in case' is strongly discouraged [22–24, 26]. Topical antiseptic therapy is a more valid 'just in case' choice; however, prior cytology is always recommended [1].

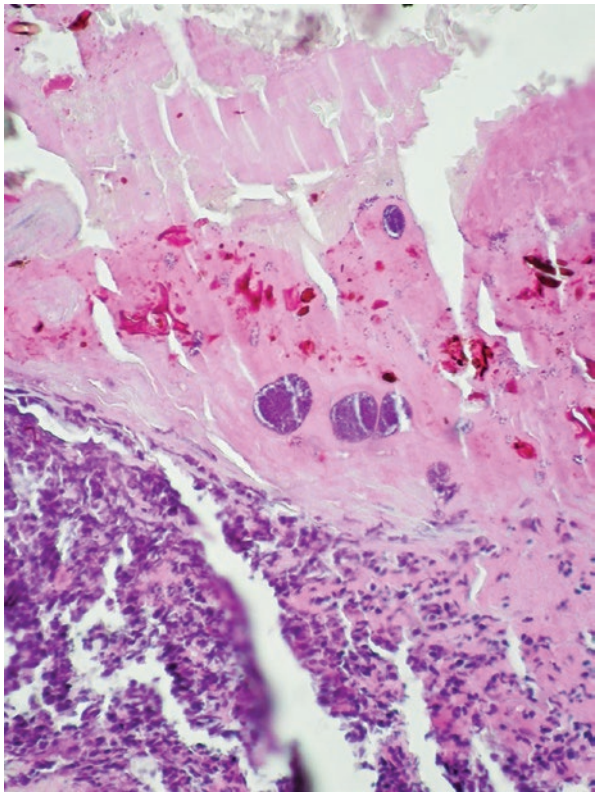

Fig. 5 Bacterial colonies, usually cocci, are frequently observed in biopsies from feline cutaneous lesions with secondary bacterial infection (H&E, 400×). (Courtesy of Dr. Chiara Noli)

Topical Therapy

Although cats are often considered less tolerant of topical therapies, and even in dogs topical therapy is considered under-utilised [23], topical therapy has been recommended as the optimal sole antibacterial treatment for superficial infections whenever achievable for the pet and owner, particularly for localised or mild lesions. It is also recommended as the best option for pyoderma associated with methicillin-resistant staphylococci (MRS) [1]. Topical therapy has the advantage of more rapid lesion resolution, reduced duration of systemic antibiotics, physical removal of bacteria and debris from the skin surface and reduced impact on bystander commensals [1, 23]. The response in dogs with SBP to daily chlorhexidine spray (4%) for 4 weeks concurrently with twice weekly bathing with chlorhexidine shampoo was comparable to oral amoxicillin-clavulanic acid (amoxi-clav) [27]. Other small studies have similarly shown sole topical therapy to be effective [1].

Although a range of topical formulations are discussed for use in dogs, it is acknowledged there is limited evidence for efficacy and safety to guide optimal choices and protocols [23]. There is even less evidence in cats. However, the author has found a range of topical antiseptics and antibiotics helpful in the treatment of SBP in some cats, particularly for localised lesions. Chlorhexidine solution (2–3%

Box 1: Important Principles of Treatment for Cutaneous Bacterial Infections in Cats in Line with Good Antimicrobial Stewardship

- Have sufficient evidence to confirm a diagnosis of bacterial infection prior to instigating treatment (unless severe and life-threatening): Avoid 'just-in-case' usage.
  - Cytology is essential; culture of bacteria from a skin surface swab does not confirm infection.
- Choose antibiotics wisely, based on recommended treatment guidelines:
  - Use first-line antibiotics for empirical use, assuming relevant options exist for the confirmed infection.
  - Only use second-line antibiotics if adverse events limit use of first-line choices and if culture and sensitivity testing (C&S) supports efficacy.
  - Do not use third-line antibiotics (e.g. cefovecin, fluoroquinolones) unless C&S indicates absence of other first- or second-line choices: Avoid justification due to 'ease of use' without actively discussing first-line oral alternatives.
- Use correct dose and duration of treatment:
  - Dose at the upper end of dose range as skin blood supply is comparatively poor, and weigh patients: slightly over-dose rather than under-dose.
  - Follow duration guidelines for the confirmed infection, and re-evaluate clinical and cytological response prior to cessation of therapy.

once or twice daily), silver sulfadiazine 1% cream or mupirocin 2% ointment (twice daily) have apparent efficacy and safety [12, 13], and fusidic acid 1% viscous eye drops (Conoptal®; twice daily) may also be useful, particularly for facial/periocular lesions. Concern has been raised over the use of both mupirocin and fusidic acid in veterinary patients, potentially encouraging resistance in resident human staphylococci, and it has been recommended to restrict their use to cases without other practical choices [1, 23]. Shampoo therapy (chlorhexidine or piroctone olamine) once to twice weekly may be adjunctive for treatment or to inhibit recurrence of SBP, although it is poorly tolerated in many cats.

Excessive grooming and exacerbated self-trauma in response to topical therapies in cats, especially to ointments or creams, may sometimes limit their use. Body suits or conforming bandages may be helpful, particularly in cats with severe pruritus. Despite a common concern of owners that licking will remove topical medications, there is no evidence to confirm that grooming notably reduces efficacy of topical therapy, as lipophilic medications will be quickly absorbed after application.

Systemic Therapy

There is a lack of consensus on the most appropriate systemic antibiotics for treatment of SPB and some variation in recommendations with geographical region [23, 28]. First-line antibiotics are considered suitable choices for empirical therapy,

assuming a diagnosis is confirmed (e.g. intracellular cocci on cytology). Culture and antibiotic susceptibility testing (C&S) is important for cases that respond poorly to appropriate empirical therapy, or if there is higher risk of MRS (repeated antibiotic courses, other household pet carriers, some geographical regions) [1, 12].

Amoxi-clav and cephalexin are generally considered first-line choices for feline SBP (see later section on Antibiotic Stewardship) [12, 13]. Amoxi-clav was effective for eosinophilic plaques and partially effective for lip ulcers with concurrent bacterial infection [25]. Doxycycline is used in some countries for first-line therapy of SBP, but resistance in some geographical regions [29], and potential value for MRS and multidrug-resistant staphylococci in others [10], suggests it may be less appropriate for first-line use. There is also debate over the use of cefovecin as first-line treatment for feline SBP, and although it is commonly adopted, third-generation cephalosporins are considered critically important antibiotics in human medicine, reserved for life-threatening diseases [26, 30–32]. It has thus been recommended cefovecin is not appropriate for first-line treatment for feline SBP, unless, due to compliance issues, no other treatment is possible.

Second-line antibiotics may be considered if first-line antibiotics are not effective or serious side effects (real or potential due to previous history) limit the use of first-line choices. The major second-line choices for feline SBP are clindamycin or doxycycline, with preceding C&S optimal as efficacy is less predictable than for first-line choices (see later section on Antibiotic Stewardship). Lower sensitivity of staphylococcal isolates has been documented to clindamycin compared to amoxi-clav and cephalexin in South Africa [8] and to erythromycin in Malaysia [29]. Cefovecin is another potential second-line choice, when all avenues of oral administration of first-line and initial second-line choices have been exhausted. Second-generation fluoroquinolones (FQ) (enrofloxacin, marbofloxacin) are a final consideration, but restriction to cases with no other alternatives based on C&S is recommended. Ease of administration of FQ and low incidence of side effects are not justification for their use as first-line or early second-line options.

Third-line antibiotics are rarely indicated for feline SBP, with topical therapies, even requiring hospitalisation and/or sedation where necessary, preferable. They include third-generation FQ (orbifloxacin, pradofloxacin), aminoglycosides (amikacin, gentamicin) and rifampicin. Critical antibiotics, reserved for life-threatening infections in humans, with veterinary use discouraged, are not a consideration for treatment of SBP in any species (see later section on Antibiotic Stewardship).

Duration of Therapy

Although there is an absence of scientific evidence to confirm an optimal duration of therapy for SBP in either dogs or cats, current expert opinion recommends a 3-week therapy as most appropriate [1, 26]. Shorter courses may be considered, until clinical lesions and microbiological evidence of infection have resolved; however, re-evaluation of patients is essential to make this assessment [1, 28].

Treatment of the Primary Disease

It is well-recognised that the underlying primary cause of SBP must be managed to limit recurrence. However, there is less clarity on whether treatment of SBP and primary diseases need to occur concurrently or sequentially. As immunosuppressive therapy is contraindicated when treating infectious diseases, as a general rule, it is advised that SBP treatment be completed, prior to commencing any sustained glucocorticoid therapy (e.g. for primary allergy). In some cases of very active primary disease, resolution of SBP may not readily occur until the primary disease is more controlled. Management of primary atopic dermatitis in particular can be very challenging in some cats prone to secondary bacterial infections [13]. Ciclosporin therapy may be a more valid allergy treatment choice than glucocorticoids in this scenario, sparing innate immune responses (neutrophils, macrophages), albeit with slower onset of effect.

Deep Bacterial Infections

Chin Nodular Swelling: Secondary Deep Bacterial Pyoderma

Feline chin acne most typically presents with brown to black comedones and hair casts on the ventral chin and occasionally the margins of the lower or upper lips (Chapter, Idiopathic Miscellaneous Diseases). A proportion of affected cats develop notable swelling with draining tracts, often due to secondary deep bacterial infection. Of cats with feline acne presenting to referral hospitals in the USA, 42% had deep bacterial infection (n = 72) [33], and 45% had bacteria isolated from tissue cultures (n = 22), including all cats with evidence of folliculitis and furunculosis on histopathology. The most frequent bacteria isolated, typically in pure culture, were CoPS, followed by α-haemolytic streptococci, *Micrococcus* sp., *E. coli* and *Bacillus cereus*. Of note, *Pseudomonas aeruginosa* was isolated in heavy growth from the tissue biopsy of one healthy control cat [34].

Clinical Presentation

Deep pyoderma typically presents with large papules to nodular swelling with draining tracts (Fig. 6) and less commonly diffuse swelling. Lesions may be pruritic and/or painful, and regional lymph node enlargement can occur [3, 33, 34].

Diagnosis

Cytology from fine needle aspirates (FNA) or expressed discharge after initial surface cleansing may reveal intracellular bacteria within neutrophils and/or macrophages. Careful examination may be required as bacteria can be sparse in samples from nodular lesions despite marked inflammation.

Histopathology will typically reveal folliculitis, furunculosis and perifollicular to nodular pyogranulomatous inflammation (Fig. 7); bacteria present within follicular ostia or lumina in this setting, at least focally, confirm a diagnosis. Feline acne

Fig. 6 Feline chin acne: nodular swellings and drain tracts as a consequence of a deep bacterial infection. (Courtesy of Dr. Chiara Noli)

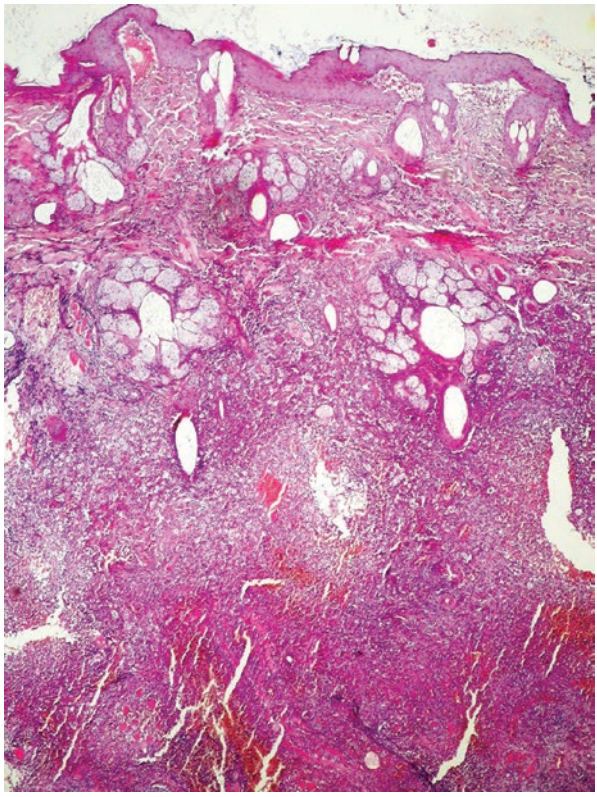

Fig. 7 Histopathological section from feline chin acne (H&E, 40×): multifocal nodular pyogranulomatous inflammation in the mid and deep dermis, mostly centred on the hair follicles, which appear completely destroyed. Haemorrhage is evident, which is reflected clinically by haemopurulent exudate. (Courtesy of Dr. Chiara Noli)

is associated with a spectrum of histopathology changes, with periglandular and/or perifollicular inflammation usually dominating. Sebaceous gland ductal dilation and pyogranulomatous inflammation of sebaceous glands are also reported [34].

The presence of folliculitis and furunculosis without causal bacteria is suggestive of a role for secondary bacterial pyoderma, but exclusion of other causes including dermatophytosis is important, and special stains are warranted.

Bacterial culture of sterile tissue biopsies or FNA from affected regions is required to identify causal species and enable antibiotic susceptibility testing.

Treatment

Systemic antibiotics are indicated; if intracellular cocci are evident on cytology, empirical treatment with cephalexin or amoxi-clav is often considered suitable. If bacterial rods are present on cytology, or in geographical regions where MRSP is more common, C&S is recommended, optimally from tissue biopsies. The optimal duration of therapy for deep pyoderma is undetermined; however, a minimum of 4–6 weeks is often advised, continuing for at least 2 weeks beyond resolution or stasis of lesions [1, 26]. Comedones typically persist in feline acne following resolution of the bacterial infection, so further treatment of the underlying pathology is important to limit recurrent infection (Chapter, Idiopathic Miscellaneous Diseases) [33].

Discrete Nodules: Bacterial Pseudomycetoma

Some bacteria rarely cause localised discrete deep infections forming skin nodules that mimic fungal or neoplastic causes. Infections presumably occur following traumatic implantation of bacteria, which are most commonly *Staphylococcus* spp., but may be *Streptococcus* spp., *Pseudomonas* spp., *Proteus* spp. or *Actinobacillus* species.

Clinical Presentation

Single or multiple inflammatory nodules, with or without draining tracts, are typical. Discharge may contain small white grains or granules, composed of compact bacterial colonies [35]. A single case with less typical overlying thick crusting is reported in an FIV-positive cat, with concurrent SBP supported by cytology findings [36].

Diagnosis

Cytology of FNA from intact nodules or impression smears of freshly expressed exudate should reveal numerous bacteria, most typically cocci but dependent on causal species. Histopathology will reveal nodular to diffuse pyogranulomatous dermatitis and/or panniculitis with numerous macrophages, multinucleate giant cells and central aggregations of bacteria, often with a brightly eosinophilic amorphous periphery (Splendore-Hoeppli phenomenon) (Figs. 8 and 9) [35, 36].

Treatment

Surgical excision/drainage is important for resolution, as systemic antibiotics will often not penetrate into the central walled-off bacteria.

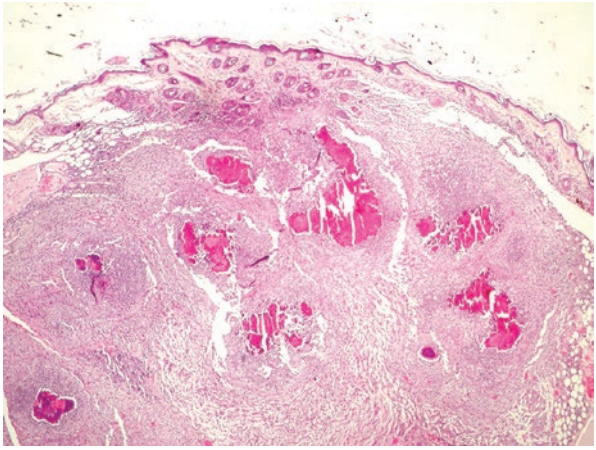

Fig. 8 Histopathological section from a lesion of bacterial pseudomycetoma (H&E 40×). There is a multifocal nodular pyogranulomatous inflammation with large bacterial colonies covered by bright red proteinaceous material, which appear clinically as white granules in the exudate. (Courtesy of Dr. Chiara Noli)

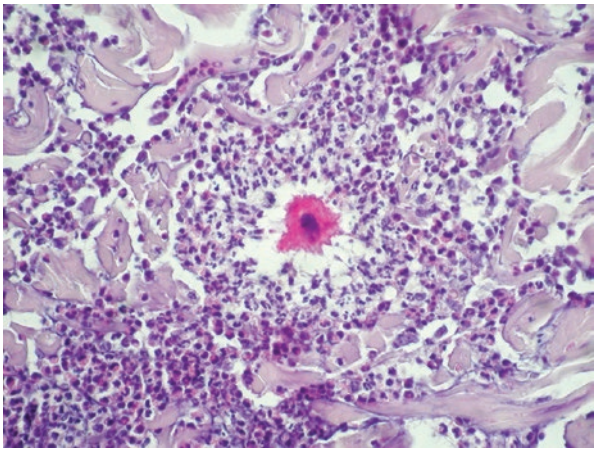

Fig. 9 A bacterial colony (dark blue in the centre, is surrounded by amorphous eosinophilic material (Splendore-Hoeppli phenomenon) (H&E, 400×). (Courtesy of Dr. Chiara Noli)

Subcutaneous Nodular Swellings with Abscessation: Anaerobic Bacteria

Painful rapidly progressing subcutaneous swellings are common in cats due to implantation of anaerobic bacteria, most typically associated with fight wounds although less commonly with other skin trauma including surgical wounds or catheterisation. Causal bacteria are often anaerobic or facultatively anaerobic oral commensals, including *Pasteurella multocida*, *Fusobacterium* spp., *Peptostreptococcus* spp., *Porphyromonas* spp. and gas-producing species such as *Clostridium* spp. and *Bacteroides* species [37].

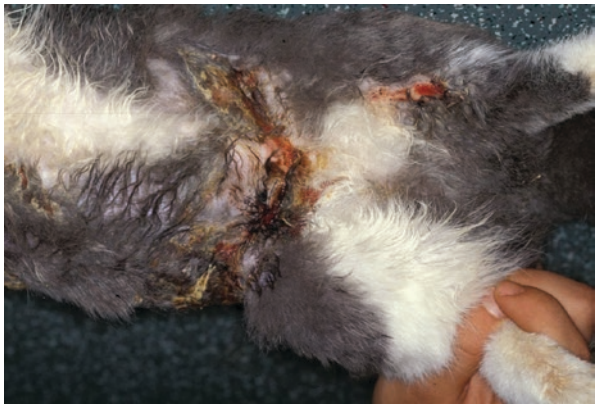

Fig. 10 Swelling, ulceration, fistulisation and necrosis of the abdominal skin of a cat due to infection with anaerobic bacteria. (Courtesy of Dr. Chiara Noli)

Clinical Presentation

Poorly demarcated areas of oedema and swelling are typical, which progress to abscessation (Fig. 10) and sometimes overlying skin necrosis. Lesions are often single, but may be multiple, and are usually painful. There is often associated pyrexia and malaise, especially with larger lesions or when bacteria produce toxins. Purulent abscess contents often have a putrid smell, and tissue crepitus may be apparent.

Diagnosis

The clinical presentation is usually diagnostic. Cytology of abscess contents, or FNA from oedematous areas in early lesions, should reveal intense neutrophilic inflammation, with bacterial rods and/or cocci often readily apparent. Mixed infections are not unusual. Culture is generally not required, but anaerobic sampling would be important to accurately identify most causal bacteria.

Treatment

Early lesions are usually managed successfully with systemic antibiotics, with most organisms sensitive to amoxi-clav or metronidazole. *Bacteroides* spp. may be resistant to ampicillin and clindamycin [30]. Surgical drainage of abscesses, with aeration and cleansing of infected tissue, is important to resolution.

Subcutaneous Nodular Swellings with Ulceration and Draining Tracts: *Nocardia*, *Rhodococcus* and *Streptomyces*

A number of bacterial species, many of which are ubiquitous environmental saprophytes, are rare causes of poorly demarcated nodular swellings with focal ulceration and draining tracts in cats. Infections are often locally invasive, and some species have a propensity to disseminate, particularly in immunocompromised cats. Most infections presumably occur following traumatic implantation.

Diagnostic tests are essential to accurately confirm the cause of this presentation. In addition to multiple potential bacteria, differential diagnoses include mycobacteria (Chapter, Mycobacterial Diseases), saprophytic fungi (Chapter, Deep Fungal Diseases) and sterile panniculitis (Chapter, Idiopathic Miscellaneous Diseases).

Cytology of FNA from oedematous tissue or fluid pockets or of smears from draining tracts (after initial skin surface cleansing) will typically reveal neutrophils and epithelioid macrophages, sometimes with multinucleate giant cells, regardless of the causal organism. Organisms will more often be detected within macrophages, with morphology varying with the causal species.

Histopathology of tissue biopsies will reveal nodular to diffuse pyogranulomatous dermatitis and/or panniculitis. Specials stains help elucidate the likely causal bacteria [38].

Bacterial culture from sterile fluid aspirates or tissue biopsies may be needed to confirm causal species and is optimal to determine antimicrobial susceptibility testing. It is important to alert the laboratory of the potential for unusual bacterial species with special culture requirements.

PCR testing can be useful for retrospectively identifying pathogens from formalin-fixed tissue samples if fresh samples are not available for bacterial culture [39].

Nocardiosis

Nocardia are ubiquitous soil and decaying vegetation saprophytes that may cause rare but potentially serious infection in cats, typically following implantation into skin wounds. Infection is more common in cats than dogs and may remain localised and indolent or be fulminant with wide dissemination; the latter course is more likely in immunocompromised hosts. *N. nova* is the most frequently identified causal species, but infections with *N. farcinica* or *N. cyriacigeorgica* also occur. Skin infections are most common, with occasional cases restricted to pulmonary or abdominal infection [40].

Clinical Presentation Progressive irregular nodules and punctate draining sinuses are typical (Fig. 11), often with concurrent malaise and respiratory signs. Skin infection may start with discrete abscesses that gradually extend into discharging, non-healing wounds. The extremities, ventral abdomen and inguinal areas are more often affected, and lymphadenopathy is common. Discharge may contain gritty granules (bacterial microcolonies) [40].

Diagnosis Filamentous bacteria that stain at least partially with acid-fast stains are typically prevalent on cytology and histopathology and appear branching or beaded (Fig. 12). Organisms may be found within clear lipid vacuoles [40]. Bacterial culture is slow; it is important to forewarn laboratories with potential cases.

Treatment Prompt early treatment of acute lesions, even in immunocompromised patients, can result in good outcomes. Surgical debridement and drainage to reduce residual organisms are optimal, and aggressive early excision, with potential later corrective surgery, is indicated. C&S is important to maximise treatment success. *N. nova* tends to have less resistance than other species and is often susceptible to sulphonamides,

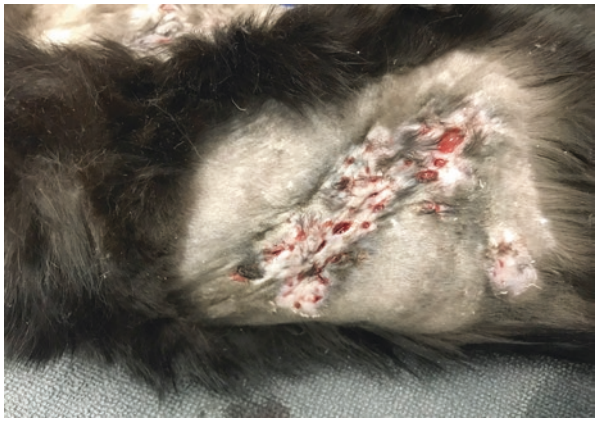

Fig. 11 Localised swelling, ulceration and training tract in a cat affected by cutaneous nocardiosis. (Courtesy of Dr. Carolyn O'Brien)

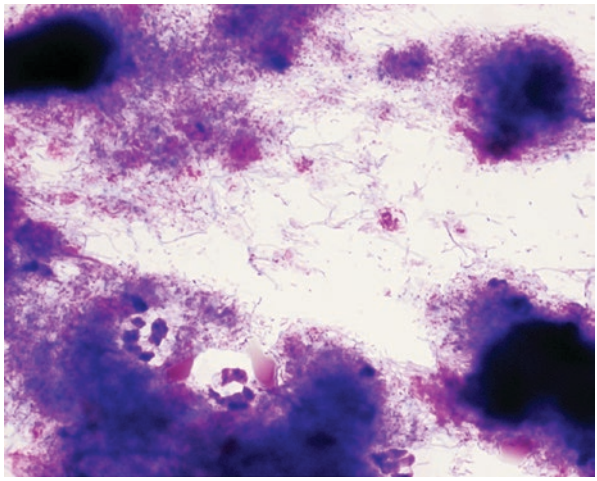

Fig. 12 Cytology of nocardiosis: multiple groups of bacteria (grains) and slender and filamentous *Nocardia asteroides* microorganisms are evident (MGG 1000×). (Courtesy of Dr. Nicola Colombo)

tetracyclines (minocycline, doxycycline), clarithromycin and ampicillin/amoxicillin, but paradoxically not to amoxi-clav (clavulanic acid induces β-lactamase production in these species) nor to FQ. Amoxicillin (20 mg/kg twice daily) combined with clarithromycin (62.5–125 mg/cat twice daily) and/or doxycycline (5–10 mg/kg twice daily) is recommended over sulphonamides. Long-term therapy is generally required (3–6 months), and recurrence is common with shorter treatment. *N. farcinica* is less commonly identified but is often multidrug resistant and highly pathogenic. Initial parenteral therapy with amikacin and/or imipenem combined with trimethoprim-sulphonamides is a consideration [40].

Rhodococcosis

Rhodococcus equi is a ubiquitous soil-borne bacterium commonly pathogenic in horses, where it produces a pyogranulomatous pneumonia and enteritis with high mortality in young foals. Infection is also increasingly documented in humans with immunocompromise and is reported in a small number of cats, involving skin (nodules with

focal ulceration and draining tracts, most frequently on the extremities), abdominal or thoracic cavities and/or the respiratory tract [41–43]. In one report, a pyogranulomatous skin disease and cellulitis (Fig. 13), different from usual presentations in cats, were described in a 2-year-old female domestic shorthaired cat [43]. Infection in local lymph nodes, presumably via lymphatic spread, is reported [41–43]. Implantation of organisms via skin wounds is proposed, with highest risk in cats with exposure to horses; infected foals shed copious bacteria into the environment via faeces [41].

Diagnosis Cytology of FNA samples and/or histopathology usually readily reveals gram-positive cocci to coccobacilli within macrophages (Fig. 14) [42, 43]. Bacterial culture is essential to confirm a diagnosis; the bacteria grow readily with aerobic culture within 48 hours, but organisms may be protected within macrophages in fluid samples, so tissue samples may be optimal [42].

Treatment C&S is important to guide potential therapy. *R. equi* infections are often refractory to conventional therapies in horses, and although a combination of rifampicin and erythromycin has been recommended, increasing resistance is rec-

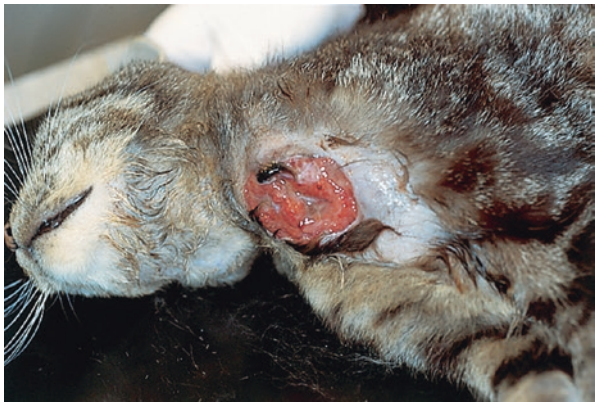

Fig. 13 Cutaneous *Rhodococcus equi* infection in a cat: pyogranulomatous dermatitis and cellulitis with superficial ulceration. (Courtesy of Dr. Anita Patel)

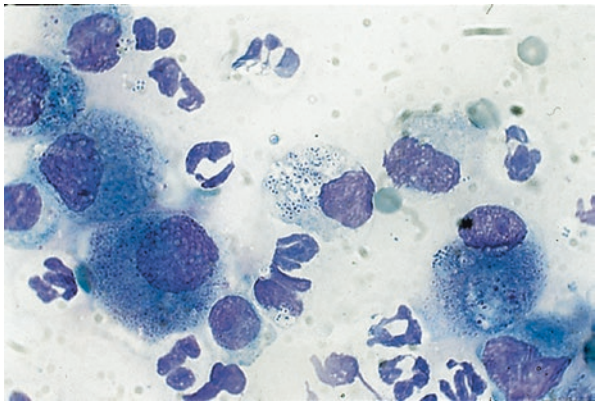

Fig. 14 Cytology of case in Figure 13: intracellular *Rhodococcus equi* organisms are evident in macrophages (MGG 1000×). (Courtesy of Dr. Anita Patel)

ognised [28]. In a confirmed feline case with a chronic limb lesion, *R. equi* displayed intermediate sensitivity to amoxi-clav, rifampicin and erythromycin and sensitivity to cephalexin and gentamicin, but the cat deteriorated despite initial cephalexin and later surgical debridement and gentamicin therapy and was euthanised [42]. In another case with sensitivity reported to doxycycline, enrofloxacin and cefuroxime, response to enrofloxacin and later doxycycline was poor [43]. However, doxycycline was reported effective in thee kittens with *R. equi* pneumonia, from two litters in a cattery in Australia where the source of the infection was undetermined [41].

Streptomycosis

Streptomyces spp. are ubiquitous environmental bacteria that very rarely cause irregular nodular lesions with draining tracts and dark tissue granules on the limbs and ventral abdomen of cats. One cat without skin lesions had mesenteric and lymph node infection. Two cats were FIV and/or FeLV positive and two cats had unknown viral status [38].

Diagnosis Gram-positive rods to coccobacilli were present on cytology and histopathology, and bacteria were identified by PCR testing [38].

Treatment All four cats failed to respond to surgical and/or multiple antibiotic therapy and were euthanised following 6–18 months of disease [38].

Dermatophilosis

Dermatophilosis is a contagious and potentially zoonotic disease caused by *Dermatophilus congolensis,* which most commonly affects cattle, sheep and horses in tropical and subtropical climates. The organism does not survive readily in the environment, and infected or carrier animals are the main source. Infection is reported very rarely in cats. Two presumptive cases presented with nodular swelling and draining tracts overlying infected lymph nodes, with associated skin surface crusting. Characteristic gram-positive branching filamentous bacteria were evident on histopathology, and both cats resided on farms in tropical northern Australia. Surgical excision was curative in one cat, and the other cat was euthanised prior to diagnostics [44]. *Dermatophilus congolensis* was isolated in pure culture from crusts in another cat presenting with crusting and exudation on the ventrolateral lip margins; it was reported sensitive to oxytetracycline and penicillin, but resistant to ampicillin, amoxicillin, gentamicin and cefoperazone [45]. Characteristic filamentous branching bacteria (Fig. 15) were present on cytology from a fourth cat with draining tracts on two lower limbs; bacterial culture was negative, but the cat responded completely to amoxicillin therapy for 10 days [46].

Streptococcal Infection

One case of extensive oedematous swelling with multifocal ulceration and draining tracts is reported on the hindlimb of a cat, associated with numerous clusters and chains of gram-positive cocci, identified by tissue PCR as *Streptococcus* spp., in skin

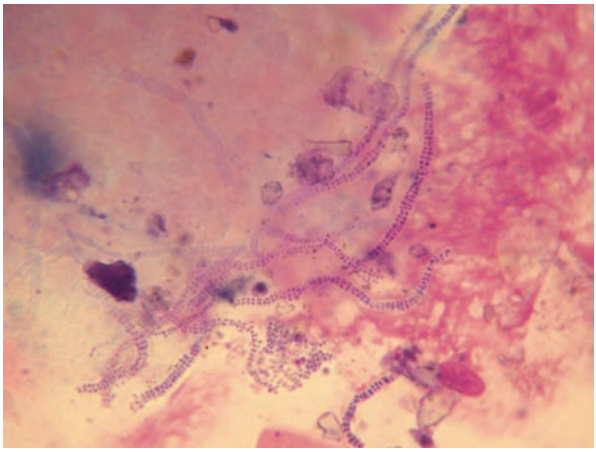

Fig. 15 Cytology of *Dermatophilus congolensis*: long colonies, like train tracks, are characteristic (Diff Quik, 1000x)

and underlying bone. Clusters of bacteria surrounded by eosinophilic amorphous material (Splendore-Hoeppli phenomenon) were present on histopathology [39].

Actinomycosis

Actinomyces spp. are oral saprophytes in a variety of animals including dogs and cats, which are most commonly associated with soft tissue and bone infections in the jaws of cattle. Rare cutaneous infections are reported in dogs, characterised by nodular swellings with discharge, typically on the extremities. Although abdominal infection with *Actinomyces* spp. is documented in one cat, and isolation of *Actinomyces* spp. is reported concurrently with other bacterial species, or from lesions without concurrent histopathological confirmation, there are no confirmed reports of *Actinomyces* spp. causing cutaneous infections in cats [47, 48].

Rapidly Progressive Oedematous Swelling to Necrosis and Septic Shock: Necrotizing Fasciitis

Necrotizing fasciitis is a rapidly progressive and frequently fatal syndrome caused by severe bacterial infection of subcutaneous tissue (fascia) and adjacent skin, typically associated with septic shock. *Streptococcus canis* is a recognised cause of fulminant disease in humans and dogs and has also been associated with an outbreak of fatal necrotizing fasciitis in shelter cats in southern California. Clonal bacteria were identified and spread via close physical contact was proposed. *S. canis* is a normal inhabitant of the urinary, reproductive and gastrointestinal tracts of dogs and cats, and although infections are rare and most typically associated with immunocompromise, necrotizing fasciitis can occur in immunocompetent hosts. In contrast to dogs where *S. canis* is mainly associated with skin infections, respiratory tract infections are more typical in cats [49]. One case associated with *S. canis* in a single cat following minor limb trauma is also reported [50].

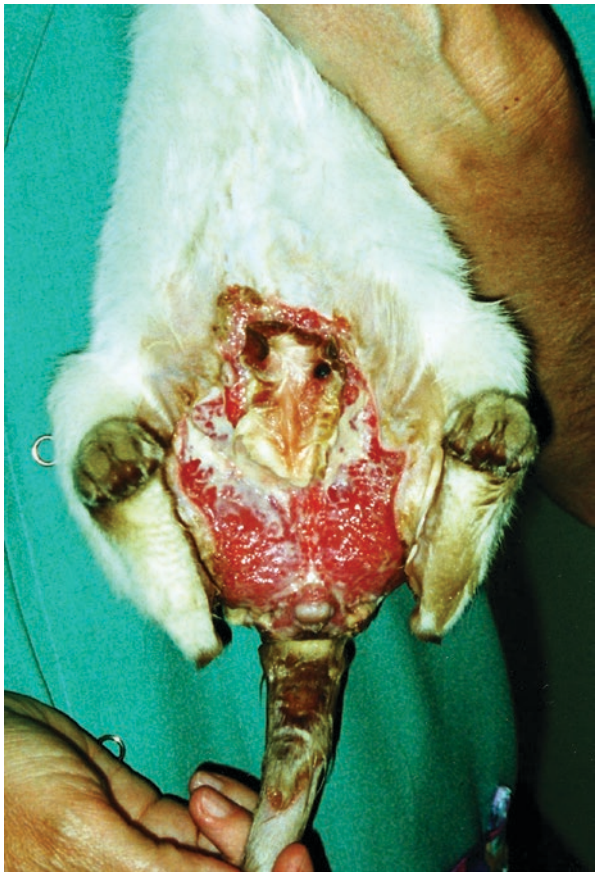

Fig. 16 Large areas of necrosis and ulceration in a cat with necrotising fasciitis. (Courtesy of Dr. Susan McMillan)

Another form of necrotizing fasciitis in people, occurring after minor skin trauma (catheterisation, hospitalisation), has been associated with multiple concurrent bacteria including *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp. and *E coli*. Single case reports in cats are described due to *Acinetobacter baumannii* [51] and multiple bacteria (*E. coli*, *Enterococcus* sp. and *S. haemolyticus*; *E. coli*, *Enterococcus faecium* and *S. epidermidis*) [52, 53].

Clinical Presentation Poorly demarcated painful regions of oedema and erythema are typical, associated with rapid development of signs of septic shock (pyrexia, severe malaise, collapse). Skin lesions progress to large areas of skin necrosis (Fig. 16).

Diagnosis FNA of affected regions reveals neutrophilic inflammation, and causal bacteria are usually apparent intracellularly within neutrophils. Bacterial culture of sterilely collected fluid or tissue samples is required to confirm the causal species. It is important to interpret culture results in conjunction with bacterial morphology from cytology and/or histopathology, as contaminant species may be cultured from exudative lesions.

Treatment Most cases reported in cats have been fatal. Urgent extensive surgical debridement, with removal of the bacterial nidus and all necrotic tissue to limit further extension along fascial planes, is recognised as crucial for suspected cases prior to availability of diagnostic test results, together with broad-spectrum intravenous antimicrobial treatment and critical care. Reconstructive surgery may be required after recovery [50].

Diagnostic Tools for Feline Cutaneous Bacterial Infections

Clinical Lesions and Historical Features

Prior to reaching for diagnostic tests, careful clinical examination and history taking for each case can focus the diagnostic possibilities and guide the most appropriate test choices. Knowledge of the more likely differentials for specific skin lesions, and the major differentials when bacterial infections are being considered, is helpful (see Table 1).

Cytology

Cytology is often the most useful initial test when considering bacterial dermatoses and may confirm a diagnosis. The most suitable technique will vary with the clinical lesions (see Table 1).

Adhesive tape impressions are suitable for all superficial skin lesions, including alopecia, scaling, crusting, excoriations, ulceration and papules. More exudative lesions can be gently blotted with a dry gauze swab prior to sampling. Good quality adhesive tape (clear, transparent, strongly adhesive; 18–20 mm width) is optimal for use on standard glass slides. Tape strips (~5–6 cm long) are pushed firmly onto lesional skin, squeezing gently on intact papules or plaques and repositioning repeatedly until adhesiveness reduces. Tapes are stained with a Romanowsky stain (e.g. Diff-Quik®) without initial fixation (dissolves the adhesive, reducing clarity). Use of the red stain is useful in cats to aid identification of eosinophils. Tapes can be dipped into stain pots, as for glass slides (Fig. 17).

Glass slide impressions are suitable for moist lesions, including erosions and ulcers, and for sampling pustules after rupture with a sterile needle. Slides are stained with a Romanowsky stain including the fixative. Heat fixing is not required.

Fine needle aspirates are suitable for deeper lesions, including larger papules and nodules. The skin surface should be gently disinfected with alcohol prior to sampling. Aspirated samples are quickly sprayed from the hub of the needle onto glass slides using an air-filled syringe. Slides are air-dried prior to routine staining with a Romanowsky stain or with gram and/or acid-fast stains for identification of less common bacterial species.

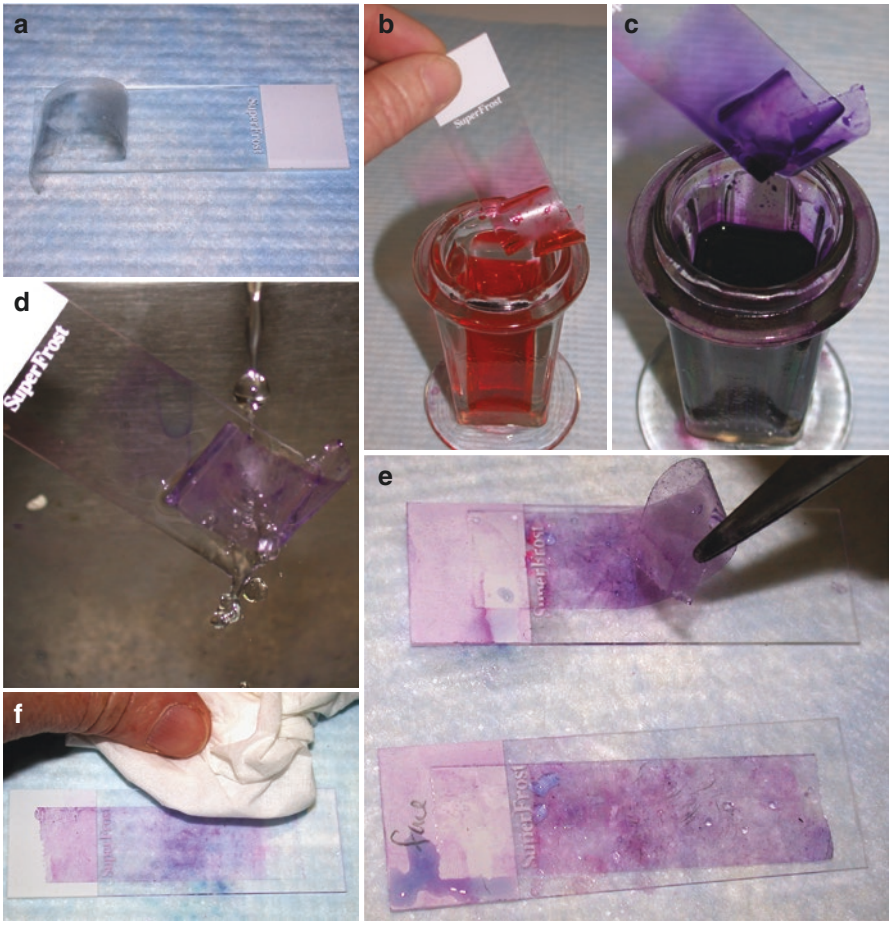

Fig. 17 Staining of an adhesive tape impression: (**a**) after sample collection, the tape is pressed firmly at one end, adhesive side down, onto a glass slide and curled into a slightly offset cylinder; (**b**) tape is dipped into red stain of Diff-Quik® (6 × 1 s dips); (**c**) tape is dipped into blue stain of Diff-Quik® (6 × 1 s dips); (**d**) stain is rinsed off tape under a gentle stream of water; (**e**) tape is uncurled by grasping free edge with forceps and laid flat on the glass slide; (**f**) tape is dried and flattened firmly onto the glass slide by wiping the surface firmly with a tissue

Interpretation of Cytology Samples Bacteria are very sparse in an oil immersion field (OIF: 1000x magnification). Oil immersion is required for accurate recognition of bacteria on normal skin surface samples despite being readily culturable from skin surface swabs (which sample thousands of OIF). The presence of increased numbers of bacteria clustered (colonising) on keratinocytes represents bacterial overgrowth (Fig. 18), while bacteria present intracellularly or closely associated within neutrophils (Figs. 19 and 20) and/or macrophages confirm infection. In deeper samples (e.g. FNA), bacteria should be absent if

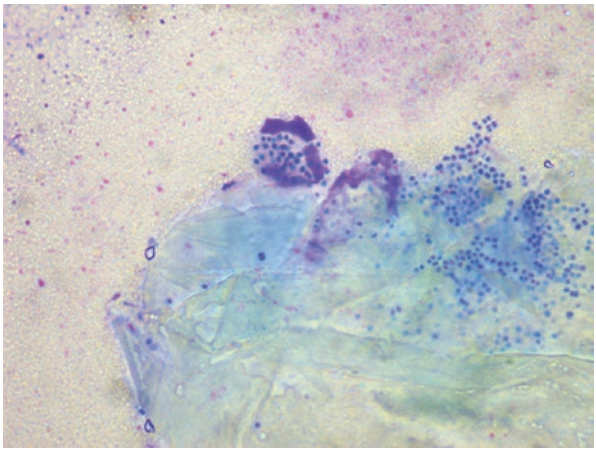

Fig. 18 Numerous cocci clustered on keratinocytes on an adhesive tape impression confirm bacterial overgrowth, while cocci intracellularly within one intact neutrophil (multi-lobed nucleus) suggest concurrent focal bacterial infection (100x lens, oil immersion; stained with Diff-Quik® as per Fig. 17)

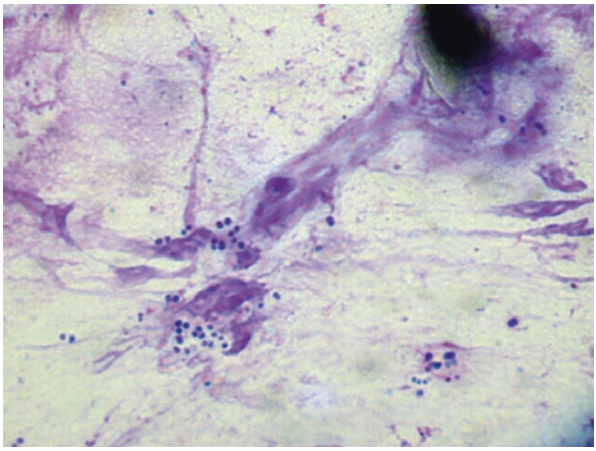

Fig. 19 Cocci intracellularly and associated with degenerate neutrophil remnants and nuclear streaming on an adhesive tape impression confirm bacterial infection (100x lens, oil immersion; stained with Diff-Quik® as per Fig. 17)

sterile technique was successfully employed; the presence of any bacteria is abnormal. Adhesive tape impressions require some experience for efficient and accurate examination. Keratinocytes typically dominate, staining pale to mid-blue and ranging from sheets of flat polyhedral cells to single or clustered shards (follicular cells). Inflammatory cells stain purple, with neutrophils most prevalent; they may be in small clusters or form peripheral rims around keratinocyte sheets. Eosinophils may also be present, particularly in cases with underlying hypersensitivity. Neutrophils should be plentiful in erosive or ulcerative samples but may be relatively sparse in drier lesions. Neutrophils degenerate quickly on the skin surface, often appearing as elongated strands of nuclear material (nuclear streaming). Tapes should be scanned under low power microscopy (4x lens) for areas of dense cells or neutrophil clusters to examine under higher power (see Fig. 20). Microscope oil is placed directly on the tape surface to examine under OIF.

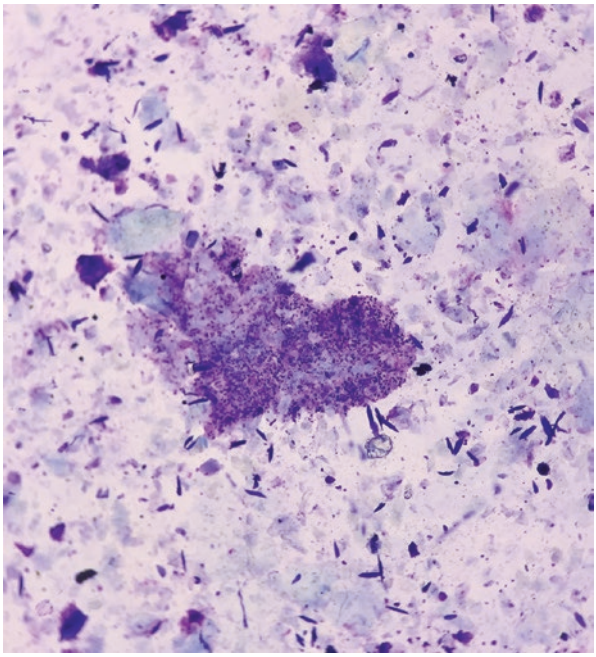

Fig. 20 Keratinocytes distributed singly and in sheets on an adhesive tape impression with a central neutrophil cluster (4x lens; stained with Diff-Quik® as per Fig. 17)

Bacterial Culture

Culture and antibiotic susceptibility testing (C&S) is vital for bacterial infections caused by species with unpredictable antimicrobial sensitivity profiles, such as rods and many of the environmental bacteria that cause sporadic deep infections. In contrast, empirical therapy based on cytology is considered appropriate for many cases of SBP [22]. C&S is indicated in severe life-threatening infections, if rod-shaped bacteria are evident on cytology (where sensitivity is less predictable), if empirical therapy does not resolve lesions or when antibiotic resistance is more likely in that geographical region or patient [1, 22]. There is no current evidence to support any negative influence of current antibiotic therapy on isolation of causative bacteria; thus, withdrawal of systemic or topical antibiotics is considered unnecessary [23].

Superficial Skin Sampling Collection of culture samples from primary lesions is optimal with pustules ruptured and papules incised with a needle prior to sampling with a culture swab, without preceding skin disinfection [22, 23]. Sterile tissue biopsy may be more reliable for papules [23]. In dogs with SBP, dry culture swabs were equally effective as moistened swabs or light scrapings for sampling a range of superficial lesions, including papules. Swabs were rubbed vigorously for 5–10 seconds on representative lesions, confirmed as SBP on cytology, without prior skin disinfection [54]. Culture swabs from the skin surface have also been well utilised for numerous feline skin culture studies sampling a range of skin lesions [5, 7, 9, 17, 19]. Swabs should be immediately placed in transport medium and

optimally refrigerated prior to transit to limit overgrowth of contaminants, particularly in warm climates.

Multiple strains of *S. pseudintermedius*, with distinct antimicrobial resistance profiles, have recently been detected from single lesions in canine SBP, with pustules and, to a lesser extent, papules associated with less species and strain diversity than collarettes and crusts. Pustules and papules were swabbed after incision with the tip of a sterile needle. Crusts and collarettes were sampled by touching a culture swab to the edges of lesions [55]. These findings reinforce the value of sampling primary lesions whenever possible and raise the potential importance of collecting multiple samples from a range of primary lesions to aid identification of all potential pathogens collectively contributing to infection in a patient.

Deeper Skin Sampling FNA or tissue biopsies collected with sterile technique are appropriate for bacterial culture from nodular lesions, with tissue samples most reliable. The surface epidermis may be excised after sample collection to help avoid isolation of contaminants. Swabs of discharging tracts are not suitable, as a range of contaminant bacteria are readily isolated [22]. When an infectious cause remains uncertain, and a range of infectious agents with varying culture requirements are differentials, tissue culture samples can be held refrigerated in a sterile container on a sterile saline-moistened swab, pending histopathology.

Culture Techniques Minimum microbiology evaluation should include complete speciation of staphylococci, regardless of tube coagulase status, and an antibiogram for all cultured isolates [1]. In-house culturing can be clinically misleading, resulting in erroneous and ineffective treatments and is not recommended, particularly for superficial skin sampling [28].

Culture Interpretation Culture results should always be interpreted in light of concurrent cytology findings and the likely pathogens in that location. Growth of bacteria in the laboratory alone does not confirm a pathogenic role. The morphology of cultured isolates must be consistent with morphology of bacteria evident on cytology for isolates to be relevant. Even bacteria with alarming multidrug resistance profiles can be inadvertent contaminants or incidental commensals, without any role in the current skin disease [1, 22]. However, correctly discerning the relevance of cultured isolates is not always straightforward; although CoPS are proposed as the major skin pathogens, commensal CoNS and a variety of environmental saprophytes may be pathogenic at times, particularly with concurrent immunosuppression [1, 22].

Histopathology

Skin biopsies for histopathology are essential to confirm a diagnosis for many deep nodular lesions. Multiple excisional biopsies are optimal, sampling any smaller

peripheral lesions in addition to large lesions and avoiding central areas of large lesions which may be necrotic. Larger lesions should be sectioned to ensure adequate formalin penetration. Biopsies for histopathology should be placed in formalin immediately after collection. Biopsy samples can also be retained frozen for potential PCR or other molecular testing.

Histopathology is less often indicated for superficial infections but may be important where cytology results are inconclusive or presentations are atypical for SBP. Punch biopsies are suitable for small lesions (pustules, papules) or uniform lesions (plaques, erythema, crusting). Elliptical samples are most useful for transitional areas and edges of ulcerative lesions.

PCR Testing

PCR testing can be helpful to identify species not readily culturable in the laboratory. It is ideally performed on fresh tissue biopsies, collected with sterile technique, but can also be performed on formalin-fixed samples, assuming fixation in formalin was for <24 hour. PCR detection from swab samples does not confirm any role as a pathogen for environmental bacteria (e.g. *Nocardia* spp.) as detection may simply reflect skin contaminants.

Treatment Principles for Feline Cutaneous Bacterial Infections and Antimicrobial Stewardship

Antimicrobial Resistance and Stewardship

Increasing development of antimicrobial resistance is of profound concern in recent years and has marked impact on human and animal health and related economics. It is undeniable that antimicrobial use can result in antimicrobial resistance in the species that is being treated and that some resistant pathogens or resistance mechanisms can be transmitted bi-directionally between animals and humans [1, 28, 56].

Methicillin resistance of *Staphylococcus* spp. relevant to veterinary medicine has been recognised as a serious problem worldwide since the late 1990s, with geographical variation in incidence, but rapid escalation of resistant *S. pseudintermedius* (MRSP), *S. aureus* (MRSA) and *S. schleiferi* species. Acquisition of methicillin resistance confers resistance to all β-lactam antibiotics, including cephalosporins. MRS isolates also frequently acquire co-resistance to other classes of antibiotics, especially FQ and macrolides [18, 19]. MRSP in particular is not uncommonly multidrug resistant (resistance to at least six antibiotic classes). As *S. pseudintermedius* is a major canine pathogen and a recognised feline pathogen, this has created significant new veterinary challenges [1].

Inappropriate use of antibiotics in the veterinary arena is considered an important factor promoting progression of resistance [1, 28, 56].

- **Cefovecin:** Despite being reported as the most frequently chosen antibiotic for use in cats in recent studies, and specifically the most frequently used for skin infections or abscesses, it is a third-generation cephalosporin, which is considered 'highest priority/critically important antimicrobials' in human medicine, reserved for life-threatening infections or when culture and susceptibility testing does not indicate alternate antibiotic choices [26, 31]. Reported use is often 'just in case', without any clinical and/or cytological evidence to confirm a role for bacterial infection [31]. Alarmingly, only 0.4% of prescriptions in >1000 cats had C&S testing performed at the time of use and none prior to use. In addition, nearly 23% had concurrent glucocorticoid treatment, with long-acting methyl-prednisolone acetate injections in 38% of these, although these drugs are contraindicated in the face of active infections [31]. Prescription of cefovecin due to convenience of administration is not a justification for valid use.
- **Fluoroquinolones:** There is evidence that FQ therapy can promote colonisation with bacteria carrying more resistance genes. FQ therapy was a significant risk factor for isolation of MRS, multidrug-resistant staphylococci, and FQ-resistant staphylococci from mucosal samples in dogs in a recent study in England [56]. Clindamycin and amoxi-clav therapy were not significantly associated with detection of antibiotic resistance, but cephalexin was, potentially due to longer treatment courses typically used in contrast to amoxi-clav. FQ maintained this effect at 1 month post-treatment and cephalexin until at least 3 months post-treatment [56]. FQ should not be used as first-line treatment options.

Feline MRS Infections There are increasing reports of MRSP and MRSA skin isolates from cats with skin lesions, although rarely with confirmed pyoderma, in multiple regions of the world [6, 8, 10, 57]. Variable co-resistance of isolates is documented, including MRSA with FQ resistance (11.8%) in Australia [10], MRSP with multidrug resistance in Thailand [57] and MRSP also resistant to TMS (30.8%), chloramphenicol (7.7%) or clindamycin (7.7%) in Australia [10]. MRSP isolates from cats are typically sensitive to rifampicin, FQ (second- or third-generation) and amikacin. CoNS that are more frequently isolated in cats are also often methicillin-resistant and multidrug resistant [6].

Risk factors increasing the likelihood of MRS infections in cats are currently unknown. Risk factors identified in dogs include prior antibiotic therapy, eating animal stools and contact with veterinary hospitals. Despite confirmed sharing of staphylococcal isolates including MRSP between pets, dogs from multidog households appear less likely to have mucosal MRS [56].

Antimicrobial Stewardship The appropriate use of antimicrobials to reduce promotion of further antimicrobial resistance is an important concept referred to as antimicrobial stewardship. The first important principle of appropriate antibiotic usage is to prescribe antibiotics only in patients with sufficient evidence to confirm a diagnosis of bacterial infection. Use of antibiotics 'just in case', especially without prior diagnostics or when diagnostics fail to confirm bacterial infection, is strongly discouraged [23, 24, 26, 30, 31].

The second important principle of appropriate antibiotic usage is wise choice of antibiotic, based on the likely causal bacteria and their likely sensitivity profiles. Empirical choice is appropriate for diseases where causal pathogens are fairly predictable and have fairly predictable antibiotic susceptibility profiles and first-line antibiotics (see later) are appropriate. Use of antibiotics that have greater value for some resistant bacteria (second- or third-line antibiotics) is not suitable without evidence from C&S that they are appropriate and first-line choices are not, unless facing life-threatening situations.

The final important principle of appropriate antibiotic usage is to use the correct dose and duration of the chosen antibiotic, taking care to weigh patients accurately prior to therapy and rounding doses up rather than under-dosing (see Table 2). Although sound evidence is lacking, it is generally recommended that treatment of superficial infections continues for 3 weeks and deep infections for at least 4 weeks (and sometimes many months for difficult pathogens). See specific diseases for further guidelines.

Antibiotic Choices

Antibiotic classes are divided into generations based on differences in their spectrum of activity [30], and they can also be divided into groups based on current prescribing guidelines. There is no clear consensus on optimal antibiotic choices for bacterial infections in either dogs or cats [1, 26, 28, 30, 31, 58], with a general paucity of scientific evidence to clarify. The following recommendations for feline cutaneous bacterial infections are based on a compilation of current expert opinion in both veterinary and human medicine.

First-line antibiotics are considered most appropriate for empirical therapy of diagnosed infections, as they are generally well-tolerated and have high efficacy against the expected causal bacteria [26]. Empirical therapy appears suitable for treatment of feline pyoderma. First-line choices for feline pyoderma are the following:

- *Amoxi-clav or cephalexin* – both reported with high levels of sensitivity to isolated *Staphylococcus* spp. [8] Even in regions where MRS are common in canine SBP, MRS infections in cats appear very rare, and most reports are of laboratory isolates [18, 19].

Second-line antibiotics should only be used when there is culture evidence that first-line drugs will not be effective or as initial empirical therapy for severe infections while awaiting C&S results if resistance to first-line drugs is more likely. This classification includes newer broad-spectrum antibiotics important to animal and human health, so reserving their use to necessary cases is prudent. Not all second-line choices are equal, with a hierarchical consideration recommended, guided by regional data [30]. Second-line antibiotics relevant to treatment of feline skin infections include the following:

Table 2 Systemic antibiotic choices for feline bacterial infections in line with antimicrobial stewardship guidelines* [26, 28, 30, 31, 58]

	First-line: potential empirical therapy (dose mg/kg, frequency)				**Second-line:** only when C&S supports use and first-line not suitable; or while C&S pending if resistance likely (dose mg/kg, frequency)				**Third-line:**only when C&S supports use and no other choices (dose mg/kg, frequency)			**Critical:** (no veterinary use)
Diagnosis	AMC (20–25 BID)	CX (20–25 BID)	DXY[a](5 BID)	METR (10 BID)	CLI (5.5–11 BID)	FQ 2[nd] Marbo (2.7–5.5 SID), Enro (5 SID)	CHL (50 BID)	TMS (15 BID)	CFV[e] (8 q 14d)	FQ 3[rd]Prado (7.5 SID) Orbi (2.5–7.5 SID)	GNT, AMK, RIF	VAN, TEI, TEL, LIN
SBP/ DBP	S[b,c]	S[b]	M	A (DBP only)	Some MSSP/MSSA Some MRSP/MRSA				MSSP/ MSSA only	Some MRSP/ MRSA	MRSP/ MRSA	
Abscess /cellulitis	S	M	M	S	S[d]	R						
Nocardia	R	R	M	R		R		M		R		
Rhodococcus	R	R	M	R							M	
Uncertain	**No antibiotics** "Just in case" use strongly discouraged[24,56]											
Side effects	GIT (mild)	GIT (more)	Oesophageal stricture (water-swallow)		GIT (mild)	Retinal degeneration (enro, higher doses)	Myelosuppression; aplastic anaemia in people handling	Blood dyscrasia		Retinal degeneration (orbi, higher doses)	Severe risk: renal, hepatic, ototoxic	

*Some regional variation acceptable: judicious antibiotic use requires consideration of local availability, veterinary licensing, recommendations for human use, and regional antimicrobial susceptibility data [1]

Antibiotic abbreviations: *AMC* amoxicillin-clavulanic acid, *AMK* amikacin, *CFV* cefovecin, *CHL* chloramphenicol, *CLI* clindamycin, *CX* cephalexin, cefadroxil; *d* day, *DXY* doxycycline, *Enro* enrofloxacin, *FQ 2nd* second generation fluoroquinolone, *FQ 3rd* third generation fluoroquinolone, *GNT* gentamicin, *LIN* linezolid, *Marbo* marbofloxacin, *Orbi* orbifloxacin, *Prado* pradofloxacin, *q* every, *RIF* rifampicin, *TEI* teicoplanin, *TEL* telavancin, *TMS* trimethoprim sulphonamide, *VAN* vancomycin

General abbreviations: *A* potential adjunctive value only: not as sole treatment, *C&S* culture and antibiotic susceptibility testing, *DBP* deep bacterial pyoderma, *GIT* gastro-intestinal tract, *M* some resistant isolates, at least in some geographical regions, *MSSP* methicillin-sensitive *Staphylococcus pseudintermedius, MRSP* methicillin-resistant *Staphylococcus pseudintermedius, MSSA* methicillin-sensitive *Staphylococcus aureus, MRSA* methicillin-resistant *Staphylococcus aureus, MSSA* methicillin-sensitive *Staphylococcus aureus, R* high levels of resistance for common causal bacteria, *S* typically high levels of sensitivity for causal bacteria, *SBP* superficial bacterial pyoderma

[a]May be best considered 2nd-line, particularly in regions where MRSP-isolates are more often susceptible to doxycycline; Minocyclin 8mg/kg once daily can be used if doxycycline unavailable/expensive

[b]Assuming intracellular cocci are present on cytology

[c]May be the choice when cocci and rods are present on cytology; C&S is indicated if rods are exclusively present on cytology

[d]Resistance occurs with some *Bacteroides* spp,. and most gram-negative bacteria

[e]Often considered second-line, or even first-line; however, third-generation cephalosporins are considered third-line in human medicine

- *Clindamycin* – registered for use in many countries for skin and soft-tissue infections. Although there is some debate in veterinary medicine, macrolide antibiotics are not first-line choices in human medicine [30]. Clindamycin has also been shown to have lower levels of sensitivity to staphylococcal isolates in some studies, and a bacterial culture and susceptibility test is recommended prior to its use [8].
- *Doxycycline* – considered first-line in some regions. However, it may be generally less suitable as a first-line choice considering that high levels of resistance are documented in staphylococcal isolates in some regions [10, 29], even though lower resistance in others [8]. Minocycline has a similar spectrum of action to doxycycline and is less expensive and more available in some countries but may be associated with more gastrointestinal irritation [30].
- *Cefovecin* – effective against some gram-negative and anaerobic bacteria in addition to gram-positive bacteria, providing a broader spectrum of activity than second-generation cephalosporins such as cephalexin. There is generally poor activity against *Pseudomonas* spp. and enterococci. Although typically considered first- or second-line in veterinary medicine, third-generation cephalosporins are considered critically important antibiotics in human medicine reserved for life-threatening diseases (third-line), so classification as second-line is questioned [30].
- *Second-generation FQ (enrofloxacin, difloxacin, marbofloxacin, ciprofloxacin)* – primarily target gram-negative bacteria, which are less frequent skin pathogens.
- *Trimethoprim-sulphonamides* – greater risk of side effects in cats and lower sensitivity of many bacteria compared to other choices reduce the suitability of this option; may be effective for some MRS.

Third-line antibiotics are very important to animal and human health, especially for treatment of multidrug-resistant bacteria, and their use should be only considered when C&S indicates a lack of other treatment choices. Many are not licensed for veterinary use [26, 30]. Their use for superficial infections is strongly discouraged. Third-line choices for cats with severe bacterial cutaneous infections include the following:

- *Third-generation FQ* (*pradofloxacin and orbifloxacin*) – have an increased gram-positive and anaerobic spectrum compared to second-generation FQ, in addition to good gram-negative coverage; considered unlikely to be effective for *Nocardia* spp. [30].
- *Aminoglycosides* (*gentamicin, amikacin*) – potential considerations only for life-threatening skin infections, but have considerable risk of severe renal side effects, requiring careful monitoring, concurrent fluid therapy and brief duration therapy

- *Other new and old antibiotics* (*chloramphenicol*, *clarithromycin*, *rifampicin*, *imipenem*, *piperacillin*) – potential use for MRS and multidrug-resistant bacteria, but considerable potential for moderate to severe side effects
- *Newest generation antibiotics* (e.g. *vancomycin, teicoplanin, telavancin, linezolid*) – deemed of critical importance to human health and strongly discouraged/unavailable for veterinary use [1, 26]

Management of Veterinary Patients with MRS Infection

Transmission of MRS between humans and various animal species including cats is documented [1, 28]. MRSA and methicillin-resistant CoNS, including *S. haemolyticus*, *S. epidermidis* and *S. fleurettii*, were co-isolated from multiple cats, horses and humans on one farm in Europe, with isolates sharing the same characteristics [59]. Concern is thus raised when MRS infections are documented in veterinary species, when greater bacterial numbers are likely to increase the risks of transmission.

It is currently recommended that pets with MRS infections have limited contact with other pets or humans until their infections are controlled and that good hand hygiene and heightened cleaning protocols are used in the home environment to reduce potential transmission. Veterinary hospitals are also recognised as potential sources of MRS transmission, and adherence to strict hand hygiene (proper washing/drying and use of alcohol-based hand sanitizers) between handling all patients and regular cleaning and disinfection protocols will reduce the risks of transmission, with MRS susceptible to commonly used disinfectants. Barrier nursing protocols for hospitalised patients with known MRS infections are recommended [1, 56].

Despite concerns over the potential challenges of treatment of MRS infection, resistant isolates are not more virulent or likely to cause infection than non-resistant isolates. There is no current evidence to support attempted decolonisation of patients colonised by MRS, and thus, screening of clinically normal animals for carriage of MRS is currently not recommended [1].

Conclusion

Feline cutaneous bacterial infections range from common secondary to rare but potentially life-threatening deep and disseminated infections. Causal pathogens include normal skin and mucosal commensals and a range of environmental saprophytes. Development of antimicrobial resistance, particularly methicillin resistance in staphylococci, poses increasing veterinary challenges. Accurate and efficient

diagnosis is important to expedite appropriate treatment and to limit further promotion of antibiotic resistance by restricting use of antibiotics to patients with confirmed disease.

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