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Review article

_Acinetobacter in Veterinary Medicine with emphasis on A. baumannii_

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Highlights

- _A. baumannii_ can harbour many antibiotic resistance mechanisms
- _A. baumannii_ is responsible for outbreaks worldwide in both human and animals
- Animals may play a role as reservoir for *A. baumannii*
- It is of importance to implement control measures in veterinary hospitals
- Treatment should be based on in vitro antimicrobial susceptibility testing

**Abstract**

*Acinetobacter* spp. are aerobic, rod-shaped Gram-negative bacteria belonging to the *Moraxellaceae* family of the class *Gammaproteobacteria* and are considered ubiquitous organisms. Among them, *Acinetobacter baumannii* is the most clinically significant species with an extraordinary ability to accumulate antimicrobial resistance and survive in the hospital environment. Recent reports indicate that *A. baumannii* has also evolved into a veterinary nosocomial pathogen. Although *Acinetobacter* spp. can be identified to species level by the use of the matrix-assisted laser ionization time-of-flight mass spectrometry (MALDI-TOF MS) coupled with an updated database, molecular techniques are still necessary for genotyping and determination of clonal lineages. It seems that the majority of infections due to *A. baumannii* in veterinary medicine are nosocomial. Such isolates have been associated with several type of infections such as canine pyoderma, feline necrotizing fasciitis, urinary tract infections, equine thrombophlebitis and lower respiratory tract infections, foal sepsis, pneumonia in mink and cutaneous lesions in hybrid falcon. Given the potential multidrug resistance of *A. baumannii*, treatment of diseased animals is often supportive and should be based preferably on *in vitro* antimicrobial susceptibility testing. It should be noted that animal isolates show a high genetic diversity and are in general distinct in their sequence types and resistance patterns from those found in humans. However, it cannot be excluded that animals may occasionally play a role as reservoir for *A. baumannii*. In line, it is of importance to implement infection control measures in veterinary hospitals to avoid nosocomial outbreaks with multidrug-resistant *A. baumannii*.
Keywords: Acinetobacter baumannii, antimicrobial, resistance, dog, cat, horse, veterinary, review

1. Introduction

Acinetobacter spp. are aerobic, rod-shaped Gram-negative bacteria belonging to the Moraxellaceae family of the class Gammaproteobacteria. Acinetobacter spp. occupy an important position in nature because of its ubiquitous presence in diverse environments such as soils, fresh water, oceans, and sediments [1,2]. Versatile metabolic characteristics allow species of this genus to catabolize a wide range of natural compounds, implying active participation in the nutrient cycle in the ecosystem. On the other hand, multidrug-resistant (MDR) Acinetobacter baumannii causing nosocomial infections with high mortality have been raising serious concerns in human medicine. It is very likely that A. baumannii will also evolve into a serious veterinary nosocomial pathogen similar to what happened in human hospitals as its association with infections in animals is increasingly reported. The lack of attention paid to A. baumannii in veterinary medicine is particularly worrying, as there are now reports indicating the presence of similarly or even identical successful clones in both humans and animals [3,4,5]. Despite this, data regarding A. baumannii of animal origin are still scarce [4]. Of importance, carbapenem-resistant A. baumannii rank priority one of the considered pathogens by the World Health Organization according to a recent publication [6].

This review aims to provide an overview of the A. baumannii epidemiology in animal species relevant to veterinary medicine. As numerous harmless non-baumannii Acinetobacter species occur in the environment and possibly in animals, identification of A. baumannii should be based on well validated methods like e.g. rpoB sequence analysis and matrix-assisted laser ionization time-of-flight mass spectrometry (MALDI-TOF MS) coupled with an updated
database [7,8]. In the present review we used “Acinetobacter spp.” if species identification was not defined or obtained with sufficiently powerful methodologies (Table 1).

2. The Bacterium

Nowadays, the genus *Acinetobacter* comprises more than 50 validly named species. Of note, many comprise only one strain and their ecology is not well known. They belong to the γ-Proteobacteria and Pseudomonadales order and comprise a group of genetically related sugar-non-fermenting, oxidase-negative Gram-negative and strictly aerobic cocco-bacilli [1,9,10]. The genus includes both non-pathogenic and pathogenic species [1,11]. Among them, *A. baumannii* is the most clinically significant *Acinetobacter* species that is implicated in human nosocomial infections. However, *A. pittii* and *A. nosocomialis* are also increasingly reported as causes of infections [10]. It should be noted that development of molecular methods in the last 10 years also allowed a better identification of *Acinetobacter* species, and particularly of species of the *Acinetobacter calcoaceticus-Acinetobacter baumannii* (ACB) complex. For up-to-date information regarding the current taxonomy of the *Acinetobacter* genus please visit the website http://apps.szu.cz/anemec/Classification curated by prof. Alexandr Nemec.

The clinically relevant species are mostly confined to the ACB complex: *A. baumannii*, *A. calcoaceticus*, *A. pittii*, *A. nosocomialis*, and the recently added species *A. seifertii* and *A. dijkshoorniae* of which *A. baumannii* is the most important one [12, 13]. Due to the association of MDR *A. baumannii* infections with high mortality, the bacterium has also been classified as an ESKAPE organism (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), a group of pathogens with a high rate of antimicrobial resistance that are responsible for an important part of human nosocomial infections [1,14]. Originally, three international *A. baumannii* clones (the so-called
International or European clones I, II, and III with preference of the use of International clones (IC) have been reported from hospitals [15-18]. With the introduction of the multilocus sequence typing (MLST) [19], these clones I, II, and III have been shown to belong to specific sequence types (STs) which mainly cluster into three clonal complexes (CC)1, CC2 and CC3. There are two MLST approaches, the Pasteur [20] and Oxford [21] schemes and both of them can identify IC.

Little is known about the natural occurrence of *Acinetobacter* species in animals or whether animals truely are a reservoir from which spread to humans occurs. It should be noted that some *Acinetobacter* spp. are commensal in animals as they may also represent the normal flora in humans, but these *Acinetobacter* spp. seem to be unrelated are in general distinct in their sequence types and resistance patterns from those found in humans. It is therefore important to use appropriate identification and genotyping methods in order to obtain comparable data. In this regard, the type of methodologies used in projects studying *Acinetobacter* sp. from animals is listed in Table 1 to determine whether *A. baumannii* has been correctly identified and whether results are reliable to evaluate the zoonotic aspect of *A. baumannii*.

### 3. Antimicrobial Resistance and Pathogenesis

*A. baumannii* has become one of the most problematic hospital-acquired human pathogens in the last two decades due to its ability to survive in the healthcare environment and to overexpress intrinsic β-lactamases, multidrug resistance efflux genes, as well as accumulate additional antimicrobial resistance traits [10,24]. Overexpression of chromosomally located β-lactamases like the AmpC cephalosporinases (also known as ADCs [Acinetobacter-Derived Cephalosporinases]) and the OXA-51-like oxacillinases have been associated with insertion sequence (IS) elements (e.g., ISAba1 and ISAba3) next to the genes [10,25,26]. Furthermore,
efflux pumps belonging to the resistance nodulation division (RND) family are particularly
effective in generating resistance, as they form a tripartite complex together with the
periplasmic proteins belonging to the membrane fusion protein (MFP) family and the outer
membrane protein (OMP) channels, so that drugs are pumped out directly to the external
medium [27,28]. The RND efflux complex in *A. baumannii* — AdeI (the MFP), AdeJ
(transporter), together with AdeK (OMP) — was found to confer resistance to β-lactams,
aminoglycosides, fluoroquinolones (FQs) and structurally unrelated compounds [29]. The first
member of the RND family of exporters discovered in *A. baumannii* was the AdeABC system,
which is known to pump out mostly aminoglycosides, tetracyclines, macrolides and FQs
[10,30,31]. In addition to these resistance mechanisms, *A. baumannii* may acquire other
resistance genes which specify for aminoglycoside-modifying enzymes, tetracycline efflux,
sulfonamide resistance dihydropteroate synthase, and carbapenemases [10,32-35]. Among the
carbapenemases which are specific β-lactamases able to hydrolyze almost all classes of β-
lactam antimicrobials [10], the OXA-type carbapenemases (OXA-23, OXA-24/40, OXA-58-,
OXA-143-, OXA-235-group), as well as the KPC and NDM carbapenemases have already been
acquired by human *A. baumannii* isolates seriously compromising the treatment outcome
[2,3,10,36-38]. Of concern, carbapenem resistance is nowadays becoming common, accounting
for the majority of *A. baumannii* strains in many hospitals over the world [10] with colistin
(polymyxin E) remaining the last-resort antimicrobial [24]. The emergence of colistin-resistant
*A. baumannii* is a serious public health concern as it limits the therapeutic options for patients
[39]. Colistin resistance has been attributed to the loss of the LPS and to mutations into the
PmrAB operon which lead to the addition of phosphoethanolamine to the lipid A region of LPS
through the activation of the phosphoethanolamine transferase PmrC [40,41].
Carbapenem resistance has been identified in different *Acinetobacter* species from animals including *A. baumannii*, the majority of them being associated with clinical infection cases (Table 2).

Tracking antimicrobial resistance genes in *A. baumannii* as well as in other *Acinetobacter* species from animals revealed that they share common genes and genetic elements as those isolated from humans (Table 2). Among the isolates which acquired a carbapenemase gene, *bla*<sub>OXA</sub>-23 seems to be the most promiscuous since it has been identified in different animal hosts associated with transposons and plasmids, whereas *bla*<sub>NDM</sub>-1, *bla*<sub>IMP</sub>-1, *bla*<sub>OXA</sub>-58, *bla*<sub>OXA</sub>-72 were so far sporadically identified in different *Acinetobacter* species. In addition to acquired carbapenemases, these isolates may also contain resistance genes conferring resistance to other classes of antimicrobials like the aminoglycosides, tetracyclines, sulphonamides, phenicols, and macrolides (Table 2). Additionally, a few studies reported the presence of colistin resistance in *Acinetobacter* spp. from meat but the resistance mechanisms have not been characterized [42, 43]. It should be noted that the number of studies characterizing the antimicrobial resistance mechanisms of *Acinetobacter* from animal origin is still very low compared to the large number of studies which reported resistance genes in isolates from humans [33,35,38,44,45].

Bacterial factors known to play a role in the pathogenesis of *A. baumannii* are numerous and versatile likely contributing to its ability to survive and adapt in different environments and also cause a variety of infections in both humans and animals [33,46,47]. The virulence factors include porins, surface structures like capsular polysaccharides and lipopolysaccharide, phospholipases, iron acquisition systems, outer membranes vesicles, protein secretions systems, regulatory proteins, biofilm-associated proteins, as well as several different types of binding proteins and metabolic and survival profiles like utilizing peptide nitrogen sources more efficiently and the thickness of biofilms formed, respectively [33,46,47]. Alterations in cell wall synthesis [the UDP-N-acetylmuramate-L-alanine ligase (MurC) protein] and upregulated
virulence-associated proteins (OmpA and YjjK) are proteins suggested to be fundamental for pathogenesis and virulence in the airways [48].

The demonstrated ability of nosocomial isolates to grow as biofilm on both biotic and abiotic surfaces is believed to play a significant role in their persistence and antimicrobial resistance [31,49]. Consistently, although biofilm-infected wounds did not show marked differences in wound closure, the repaired skin demonstrated a disrupted epidermal barrier function [50]. This altered function was associated with two putative acyltransferases in A. baumannii designated LpxLAb and LpxMAb, which transfer one and two lauroyl (C12:0) acyl chains, respectively, during lipid A biosynthesis. LpxMAb-dependent acylation of lipid A is essential for A. baumannii desiccation survival, a key mechanism for survival in hospital settings [51]. Of note, iron starvation is not sensed as an overall biofilm-inducing stimulus by A. baumannii illustrating the impressive iron withholding capacity of this bacterium [52].

4. Species identification and Genotyping

Acinetobacter of the ACB complex can be identified to species level by the use of the MALDI-TOF MS. Of note, MALDI-TOF MS and other systems are as good as their database are, i.e. they should include reference strains of all species, preferably multiple strains per species to cover the variation within species. As a consequence, the MALDI-TOF MS allows the identification of A. baumannii, A. pittii and A. nosocomialis with acceptable accuracy. It does not identify A. dijkshornii and A. seifertii still, but these species should also be identifiable by Maldi ToF once their mass spectra introduced into the database [53-55]. However, molecular techniques are still necessary to insure unambiguous species identification [56].

The use of OXA-51 as a target gene has been advocated, but is not recommended since it may lead to false identification due to amplification of variants and presence of plasmid-located blaOXA-51-like genes in A. nosocomialis and in some non-baumannii Acinetobacter species like in
one clone of *Acinetobacter* genomic species close to 13TU [57,58]. Additionally, multiplex PCR showed atypical *bla*OXA-51-like amplification products in three clinical *A. baumannii* isolates Ab-508, Ab-511, and Ab-653 recovered from South Africa, South Korea, and Turkey, respectively [58]. Multiplex PCR targeting either *gyrB* alone or in combination with internal fragments of the 16S–23S rRNA intergenic region and the *recA* gene has been shown to be useful to differentiate *A. baumannii*, *A. pittii*, *A. calcoaceticus* and *A. nosocomialis* [59-61]. Molecular methods have also been developed for genotyping and distinction between genetically diverse strains. These methods include whole-genome sequencing (WGS), PFGE, multi-locus variable-number tandem repeat analysis (MLVA), amplified fragment length polymorphism (AFLP) analysis, RNA spacer fingerprinting, rapid amplification of polymorphic DNA (RAPD), repetitive extragenic palindromic PCR (rep-PCR), single locus genotyping (e.g., *rpoB*, *adeB*, *gyrB*, *recA* and *bla*OXA-51-like genotyping), trilocus sequence typing (3LST) (*ompA*, *csuE* and *bla*OXA-51-like genes), and multi-locus sequence typing (MLST) [12,62-65]. Currently, both the Pasteur and Oxford MLST schemes remain the most widely used genotyping methods for the characterization of *Acinetobacter* spp., although the WGS will soon become essential, especially in outbreak situations [12]. So far, PFGE and PCR fingerprinting methods still represents methods with high resolving capacity to identify clones [63,66]. Other rapid molecular diagnostic methods like the single-locus-sequence-based typing of *bla*OXA-51-like genes have been used for rapid assignment of *A. baumannii* clinical isolates to IC lineages and multilocus broad PCR coupled with electrospray ionisation mass spectrometry (PCR/ESI-MS) has been developed as an alternative to MLST [2,67-71]. Furthermore, phenotypic features and antimicrobial spectra as well as plasmid typing and resistance island typing may be useful to some extent for epidemiological studies [65]. All these different epidemiological methods have been evaluated and discussed in a recent review according to the setting of application and the type of investigation like population structure studies,
epidemiological studies, as well as local- and large-scale investigation of A. baumannii dissemination and outbreaks [70].

5. Zoonotical aspects

The last two decades witnessed a surge in the incidence of infections due to several highly antimicrobial-resistant bacteria in hospitals worldwide. A. baumannii is one such organism that can develop from an occasional respiratory pathogen into a major nosocomial pathogen [1,10]. MDR A. baumannii belongs besides methicillin-resistant Staphylococcus aureus to the most frequently isolated bacteria during outbreaks in burn units, where they were also recovered from staff and environmental samples [72]. Outbreaks within a hospital may also be caused by several different A. baumannii strains including those resistant to carbapenem which may be introduced repeatedly or maintained in hospitals unnoticed. This emphasizes the need for molecular typing to trace back potential sources of the isolates and implement infection control interventions [73,74].

It has been stated that animals can be a potential reservoir for A. baumannii and contribute to the dissemination of new emerging carbapenemases [75]. However, clear evidence demonstrating that the role of animals for the dissemination of Acinetobacter spp. to humans is lacking. Nevertheless, the situation may be different between the food producing animals and the companion animals, which are more in direct contact and vicinity with humans and more prone to transfer or acquire A. baumannii. Additionally, studies reporting Acinetobacter sp. in food-producing animals were made with healthy animals, while those of A. baumannii in companion animals include both carriage as well as clinical infection.

In food-producing animals, it has been shown that Acinetobacter sp. isolates were not MDR and lacked significant antimicrobial resistance features such as resistance islands (RIs), class 1
integrons and IS Aba1 suggesting that MDR A. baumannii found in hospitals may not have directly evolved from from such animals and from food products made thereof [76]. Another study using pulsed-field gel electrophoresis (PFGE) typing also showed that A. baumannii isolated from food-producing animals were not MDR and belonged to a different pool from those of humans [22]. However, raw meat has been found to contain A. baumannii and may still play a role as a vehicle for the transmission of this bacterium from animals to humans [42, 43]. In Switzerland, A. baumannii was present in 25% of retailed meat samples with those derived from poultry being the most contaminated (48%) [42]. Resistance to piperacillin-tazobactam, ciprofloxacin, colistin, and tetracycline was only sporadically observed (about 2-5%). The absence of resistance to carbapenem does also not support the speculation of an animal reservoir of A. baumannii with mobile carbapenemase genes. In addition, the strains were genetically very diverse from each other and belonged to 29 different STs, forming 12 singletons and 6 clonal complexes (CCs), of which three were new (CC277, CC360, and CC347). Of note, A. baumannii belonging to CC already detected in humans (i.e., CC32, CC33, CC79) were found in these meat samples, emphasizing that food cannot be excluded as a potential source for dissemination. In Portugal, different Acinetobacter spp. were detected in all the 50 meat products (chicken, turkey, pork, and beef) analysed with 166 isolates identified to belong to thirteen different Acinetobacter species [43]. The most common species was A. guillouiae (n=35) followed by A. johnsonii (n=25), and A. bereziniae (n=20). Thirty one of the 166 strains were identified as members of the A. baumannii group including A. baumannii (n = 7), A. pittii (n = 12), A. seifertii (n = 8) and A. nosocomialis (n = 4) [43]. Among the seven isolates identified as A. baumannii, one from turkey exhibited resistance to amikacin, tetracycline and colistin and one from chicken was resistant to meropenem [43]. In Lebanon, MLST analyses of Acinetobacter species from different environmental, food and animal origin revealed the presence of 36 STs, among which 24 were novel. The blaOXA-51 sequence-based gene typing
showed the presence of 34 variants, among which 21 were novel and all were isolated from animals. Finally, 30 isolates had new partial rpoB sequences indicating the high genetic diversity among *Acinetobacter* species and importance of accurate identification methods. Overall, 161 *Acinetobacter* species isolates were recovered, and among them, 42 were identified as *A. baumannii* by rpoB gene sequencing. The other identified species were *A. pittii* (n=61), *A. bereziniae* (n=10), *A. calcoaceticus* (n=4), *A. johnsonii* (n=1), *A. lwoffii* (n=1), *A. schindleri* (n=3), *A. radioresistens* (n=1), *A. beijerinckii* (n=1), *A. junii* (n=1), *A. soli* (n=1), *A. gerneri* (n=1), *A. variabilis* (n=4), as well as 30 possible novel *Acinetobacter* species. This wide variability and uniqueness of sequence types does not support the idea of animals as a reservoir of (nosocomial) *A. baumannii* either. Furthermore, *A. baumannii* was detected in 6.9% of the environmental water samples, 2.7% of the milk samples, 8.0% of the meat samples, 14.3% of the cheese samples, and 7.7% of the animal samples. All isolates showed a susceptible phenotype against most of the antimicrobials tested and lacked carbapenemase-encoding genes, except one carrying the *bla*$_{OXA-143}$[75]. Importantly, a few studies reported the presence of acquired carbapenemase genes in *A. baumannii* from food-producing animals like *bla*$_{OXA-23}$ in a cow cattle and in a pig in Lebanon and *bla*$_{NDM-1}$ in a pig in China [77,78] indicating that further attention has to be paid to this potential reservoir.

Presence of *A. baumannii* in companion animals has been investigated in clinical settings and frequently in association with infections. The prevalence of *A. baumannii* carriage was 6.5% in dogs and cats (9 carriers [2 cats and 7 dogs] out of 138 animals) in a veterinary clinic on the island Réunion, which belongs to French overseas departments [79]. In this population, hospitalization in a veterinary clinic (> one day) and antimicrobial treatment administered within the 15 preceding days were significantly associated (OR= 10.8 and 4.4, respectively) with *A. baumannii* carriage [79]. Of importance, an increase in prevalence of MDR *Acinetobacter* sp. (52 *A. baumannii*, and 3 *A. pittii*, 1 unidentified) was observed over 9 years
(from 2000-2008) in hospitalized companion animals at the Justus-Liebig-University, Germany [23]. PFGE and AFLP typing revealed the presence of IC types I, II and III suggesting possible exchange of \textit{A. baumannii} between humans and animals [23]. Similarly, nineteen clinical isolates of \textit{A. baumannii} collected from dogs (n=12), horses (n=4) and cats (n=3) in Switzerland were analysed and also belonged to IC types I, II and III [3]. Recent studies revealed the presence of acquired carbapenemase in clinical \textit{A. baumannii} isolates from companion animals suggesting that they may be related to those from humans (Table 2). In two cases of UTI in a cat from Portugal and a dog from Thailand, OXA-23-producing ST2 \textit{A. baumannii} was identified. \textit{A. baumannii} ST2 producing OXA-23 were also reported in these countries in humans indicating that such clones may be adapted to both humans and animals representing a zoonotic lineage and possible community-acquisition [39,81]. Another study revealed a possible endemicity of OXA-23-producing ST25 \textit{A. baumannii} from urinary tract infections in cats and dogs in France, but the epidemiology appeared to be independent of that of humans since ST25 \textit{A. baumannii} from humans in this country mostly harbored OXA-58 [5,82].

To date, the zoonotic role of food-producing animals as reservoir for MDR seems to be low, even if carbapenemase-producing \textit{Acinetbacter} sp. including \textit{A. baumannii} have been sporadically isolated from cattle and pigs. However, the presence of \textit{A. baumannii} in meat indicates that food may contribute to the dissemination of this bacterium in the community. On the other hand, infections caused by \textit{A. baumannii} in animals and in humans are more likely to be associated with MDR isolates which belong to the same genetic lineages, but whose epidemiological origin may differ [3, 23]. The emergence of carbapenemase-producing \textit{A. baumannii} in animals and presence of possible zoonotic lineages emphasize the importance of avoiding selection and spread of MDR \textit{A. baumannii} in animals and humans.

6. Veterinary host spectrum
The most frequently hospitalized animals are the companion animals with dogs, cats and horses being most relevant globally. As a consequence, most data regarding *A. baumannii* infections concern these animal species (Table 1). In general, these infections were commonly hospital-acquired and involved various body sites (with a slight preponderance of wound infections and abscesses). Furthermore, the majority of animals had underlying diseases and risk factors that could favour nosocomial infections [3]. Clinical and epidemiological evidence indicated that these bacterial pathogens were responsible for an increase in both morbidity and mortality with about 15 [3] to 50% [83] of systemic infections resulting in death [3-5,23,83]. As horizontal transmission of *A. baumannii* may occur from human patients to the personnel and other patients in human hospital settings [1,10,84], we emphasize that *A. baumannii* behaves to some extent as such in veterinary hospitals affecting severely ill patients, or those with an underlying condition or with indwelling devices.

6.1. Dog

A total of 7% of cultures for bacteriologic culture and susceptibility testing from canine intensive care unit (ICU) patients in the USA were positive for *Acinetobacter* spp. [85]. These samples were routinely submitted at the discretion of the clinician attending the case with input from board-certified critical care specialists. However, it should be noted that dogs also carry *Acinetobacter* spp. in their oral flora as it has been reported previously [86]. This finding underlines that *Acinetobacter* species are widely distributed in different natural niches and, apart from *A. baumannii* which developed into a clinically relevant species, the precise ecology and epidemiology of *Acinetobacter* is not well known. It is therefore not surprising that animals, which are in close contact with their environment, also carry different *Acinetobacter* species. It is therefore important to use appropriate identification methods to clearly identify the *Acinetobacter* species in cases of surveillance studies. Among the Gram-negative bacteria from
cases of canine pyoderma in Grenada (West Indies), the most common species isolated was *Klebsiella pneumoniae* (7.8%), followed by *Acinetobacter* spp. (6.9%) [87]. In addition, *Acinetobacter* spp. have also been reported in dogs with chronic eczema without clinical signs of secondary infection some time ago [88].

In a Swiss university veterinary hospital clinic, *A. baumannii* was isolated from 17 dogs over a 2½-year period, representing a proportional morbidity of 7.3 per 1,000 ICU admissions [83]. In seven dogs, *A. baumannii* induced systemic illness, whereas 10 dogs showed signs of local infection. In all animals with systemic infections, and in 2 with localized infections, *A. baumannii* contributed to the death of the animal or led to its euthanasia. The low median animal trauma triage score at presentation showed that most animals from which *A. baumannii* was later isolated were not in a critical condition or in a debilitated state. However, all the animals had at least one device (e.g., indwelling urinary catheters, chest tubes, or central venous lines) that could have served as a port of entry for *A. baumannii*. Following this report, cases of infections were continued to be recorded in the same animal hospital, with 12 dogs developing an *A. baumannii* infection [3]. The isolates belonged to two main clonal lineages (as determined by rep-PCR and MLST) which were related to sequence types of IC I and II also of importance in human medicine. Of concern is the emergence of OXA-23 carbapenemase production in genetically diverse *A. baumannii* from dogs with UTI in France and Thailand, and from vaginal and phlegmon samples from dogs in Germany (Table 2)[5,81,89-91]. The two isolates from Germany belonged to ST10 (IC8) with the *bla*OXA-23 located on Tn2008 (89), whereas the two French isolates belonged to ST25 with the *bla*OXA-23 also located on Tn2008B. The same isolates were also found in cats with UTI in both countries [5,90]. The isolate from Thailand belonged to ST2 and contained *bla*OXA-23 on Tn2006. This isolate was found to be related to an OXA-23-producing ST2 *A. baumannii* from a cat with UTI in Portugal as determined by rep-PCR (80). These canine cases were predominantly characterized by UTI (Table 1).
6.2. Cat

In a Swiss university hospital clinic, *A. baumannii* with undefined resistance profile was isolated from two domestic shorthair cats associated with intravenous catheters inserted during pre-isolation over a 2½-year period. Both cats recovered [83]. Additionally, a necrotizing fasciitis with septic shock caused by *A. baumannii* exhibiting resistance to gentamicin, FQs and tetracycline has been reported in a 4-year-old, sterilized female, domestic shorthair cat in the same hospital [92]. In Portugal, a MDR *A. baumannii* isolate caused an UTI in a 3-year-old outdoor cat presenting with dysuria and hematuria, illustrating that resistant isolates affecting felines do not exclusively circulate in hospital environments [80]. Aseptic urine culture revealed bacteriuria due to a ST2 *A. baumannii*, which has been associated with IC II. The isolate produced the OXA-23 carbapenemase and also exhibited resistance to sulfamethoxazole/trimethoprim, tetracycline, and FQs. The *bla*_{OXA-23} gene was located on transposon Tn2006. Another case of UTI caused by *A. baumannii* in a cat was also reported in Switzerland, but the isolate did not carry *bla*_{OXA-23}. In the same animal hospital, another cat developed an *A. baumannii* infection after liver biopsy. Both isolates were clonal as determined by rep-PCR and belonged to ST12 (IC II), suggesting a nosocomial source of infection. The two isolates exhibited resistance to sulfamethoxazole/trimethoprim, tetracycline, and FQs [3]. OXA-23 producing *A. baumannii* has also been reported in cats with UTI in Germany and in France [5,90]. The isolate from Germany belonged to ST1 (IC I) and carried the *bla*_{OXA-23} on a 54-kb plasmid [90]. The five isolates from France belonged to ST25 with *bla*_{OXA-23} located on Tn2008B. They were obtained from different clinics and in one of them, dogs were also affected with the same clone indicating nosocomial and community dissemination of OXA-23-producing *A. baumannii* among companion animals (5). The infected cats mainly were affected regarding UTI and skin/wounds (Table 2).
6.3. Horse

Faecal samples from 20 hospitalized horses at a teaching hospital in Belgium identified 4 not yet formally defined *Acinetobacter* species [93]. In another study from Belgium, seven *A. baumannii* were obtained from catheter tips originating from seven different horses. The organism was also isolated in pure culture from a case of thrombophlebitis [94]. Several reports indicated that the occurrence of *A. baumannii* in horses has not always been associated with disease [3,94-97]. On the other hand, *Acinetobacter* spp. sepsis and systemic inflammatory response syndrome–associated severe thrombocytopenia resulting in coagulopathy has been reported in a 48-hour-old orphan Thoroughbred colt [98].

6.4. Cattle

Of note, only one *A. baumannii* isolate was recovered from 159 faecal samples of dairy cattle in the High Plains Region of the USA [99]. It contained a chromosomal *blaOXA-51*-like variant, *blaOXA-497*, an intrinsic OXA-51 variant of *A. baumannii* that confirms species identification. In Lebanon, a clonal *A. baumannii* isolate from faecal samples from livestock (comprising pigs, fowl and cattle) was found to possess both *blaOXA-23* and *blaOXA-58* genes [77]. Samples from the same species also contained a VIM-2 carbapenemase-producing *Pseudomonas aeruginosa*. In addition, three new *blaOXA-51*-like genes (*blaOXA-148*, *blaOXA-149* and *blaOXA-150*), which have not been found previously in human *A. baumannii*, were identified in strains from bovine faecal samples [76]. Nine out of 50 faecal samples from a French dairy herd revealed *Acinetobacter variabilis* (formerly 15 TU [98]) possessing the *blaOXA-23* on a Tn2008 [100], and 2 of 45 nasal and rectal samples samples from cattle in Germany revealed *Acinetobacter indicus*-like isolates harbouring *blaOXA-23* localized on an interrupted Tn2008 transposon [101], suggesting that these *Acinetobacter* species may play a role in the dissemination of *blaOXA-23* to *A. baumannii*. One *A. baumannii* ST2 harbouring *blaOXA-23* was isolated from the feces of cattle in Lebanon [77].
6.5. Pig

Like cattle, pigs may also harbour *A. baumannii*. Healthy pigs sampled at slaughterhouses in Scotland were found to contain genetically related strains as determined by PFGE and *bla*~OXA-51~-like sequencing [76]. Compared with *A. baumannii* clinical isolates ECI, ECII and ECIII, the pig isolates had different PFGE patterns and were grouped in three different clusters (A, B and C) with genetic similarity ranging between 82% and 90%. One *A. baumannii* strain isolated in China from the lung sample of a pig with pneumonia and sepsis was found to harbor the carbapenemase gene *bla*~NDM-1~ on a plasmid [78]. In Lebanon, a *bla*~OXA-23~-producing *A. baumannii* ST491 was recovered from the feces of a healthy pig [77].

6.6. Other animals

*A. baumannii* has also been isolated from a variety of different animals with different clinical signs including rabbit, ferret, snake, rat and duck in Germany [89]. An outbreak of fatal pneumonia and acute mortality associated with *A. baumannii* has been described in a group of farmed mink in the Netherlands. Gross post-mortem examination revealed extensive haemorrhagic pneumonia in examined animals. On histology, all the lung samples showed a suppurative and haemorrhagic bronchopneumonia [102]. Another fatal case of severe fibrinous–hemorrhagic pneumonia in a mink was reported in Spain. The main lesions of an acute, severe fibrinous–hemorrhagic pneumonia were associated with proliferation of coccobacilli identified as *A. baumannii* and generalized acute–subacute congestion [103]. In about 60% of predominantly hybrid falcons admitted to the Abu Dhabi Falcon Hospital with identically localized, yellowish discolored cutaneous lesions in the thigh and lateral body wall region, *A. baumannii* was co-cultured with *Mycobacterium avium complex* [104]. Culture of a choanal swab from a captive grey parrot with progressive dyspnoea and nasal discharge in Luxemburg revealed the presence of carbapenem-resistant *A. baumannii* within a mixed
Bacterial culture. The A. baumannii isolate belonged to ST294 and contained a plasmid-mediated \textit{bla}\textsubscript{OXA-72} gene [105]. Three A. baumannii ST20, ST492, ST493 containing \textit{bla}\textsubscript{OXA-23} were recovered from the feces of fowls in Lebanon; A. baumannii ST20 also contained the \textit{bla}\textsubscript{OXA-58} gene [77].

7. A. baumannii susceptibility

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) expert rules regarding human isolates, A. baumannii is naturally (or intrinsically) resistant to the following antimicrobials: ampicillin, amoxycillin-clavulanate, cefazolin, cefotaxime, ceftriaxone, ertapenem, trimethoprim and fosfomycin [106]. Therefore, the list of antimicrobials that are usually active against wildtype A. baumannii infections is already short consisting of carbapenems (doripenem, imipenem and meropenem), polymyxins [colistin (polymyxin E) and polymyxin B], tigecycline, FQs, and aminoglycosides [107]. However, most of the above available treatment options can also be shrunk by further mechanisms of resistance due to the acquisition of mobile genetic elements (e.g., plasmids, IS elements, transposons) and/or chromosomal mutations (e.g., those in the \textit{gyrA} and \textit{parC} genes and affecting FQs)(Table 2). It should be realized that available treatment options are mainly derived from human studies.

In a recent study [108], the best approach to treat MDR A. baumannii pneumonia in critically ill patients has been assessed based on estimates of Bayesian network meta-analysis reported as rank probabilities to identify the relative rankings of antimicrobial treatments based on the surface under the cumulative ranking curve, ranging from 0% (statistically certain to be the worst treatment) to 100% (statistically certain to be the best treatment). The best approach to treat MDR A. baumannii pneumonia in critically ill patients with antimicrobials showed to be
in the following order fosfomycin + IV colistin, inhaled colistin + IV colistin, high dose tigecycline (defined as a total daily dose of 200 mg/day after a loading dose of 200 mg), and IV colistin therapy. However, resistance to these antimicrobials has also been reported and the advent of pan-drug resistance might become a very plausible and concerning scenario [1,10,24,109-111]. Carbapenem-resistant A. baumannii (especially those producing the OXA-23 carbapenemase) has become common in many hospitals. Moreover, such isolates are frequently co-resistant to all other antimicrobial families (e.g., aminoglycosides and FQs) routinely tested. Therefore, the treatment of carbapenem- and/or pandrug-resistant A. baumannii infection involves the use of combinations of last resort agents such as colistin and sometimes tigecycline, but the efficacy and safety of these approaches are yet well determined [10,112]. Of interest, a systematic review and meta-analysis favoured the clinical use of antimicrobial monotherapy in contrast to a tigecycline-based combination therapy regimen for the treatment of MDR A. baumannii infections [113]. However, the value of tigecycline combination therapy managing pandrug- or extensively drug-resistant A. baumannii ventilator-associated pneumonia needs further evaluation [114].

In veterinary medicine, there is no such standard approach and treatment of diseased animals suffering from MDR A. baumannii strains is mostly supportive and specific therapies should be preferably based on in vitro antimicrobial susceptibility testing (AST). The emergence of carbapenem-resistance in clinical A. baumannii isolates from animals should stress usage of AST. These isolates exhibit frequently a MDR profile associated with the acquisition of additional resistance genes conferring resistance to aminoglycosides, tetracyclines, and sulfonamides (Table 2), leaving colistin one of the last active antimicrobial.

In veterinary farm animal medicine, colistin has been used for decades for the treatment and prevention of infectious diseases. Colistin has been administered frequently as a group treatment for animal gastrointestinal infections caused by Gram-negative bacteria within
intensive husbandry systems. Despite its extensive use in veterinary medicine, there had been limited evidence for the development of resistance to the drug and for the transmission of resistance to colistin in bacteria that have spread from animals to humans [115]. However, resistance to colistin may occur by point mutations in A. baumannii [116], and a recent report showed the presence of a plasmid-mediated colistin resistance gene mcr-1 in Enterobacteriaceae [117]. It is likely a question of time to also see mcr-1 in Acinetobacter spp. As antimicrobial therapeutical options are also limited in veterinary medicine, to our opinion regarding treatment of diseased animals suffering from MDR A. baumannii consulting in vitro AST should be mandatory as standard approach before the use of last resort antimicrobials.

8. Vaccination

The first steps towards a vaccine against A. baumannii include the identification of antigen candidates [118]. A limitation of this approach, however, is that the strain-to-strain variation in carbohydrate structures is so great that a multivalent vaccine to target all pathogenic Acinetobacter is unrealistic [119,120].

9. Prevention

As mentioned before, members of the genus Acinetobacter are considered ubiquitous organisms [16] as Acinetobacter species prevail in natural environments, including soils, fresh water, oceans, trout intestinal contents, frozen shrimps, meat, sediments, the polar region, and hydrocarbon-contaminated sites [1,42,119,121-122]. In addition, species of the genus Acinetobacter normally reside on the human skin, oropharynx, and perineum [123] and were
recovered from human milk [125-126]. Early detection combined with ASTs and implementation of rigorous infection control measures is essential to prevent major outbreaks due to MDR A. baumannii that has a high potential to spread among patients [10,126] and staff [84]. The most likely explanation for the isolation of the same strain from consecutive patients in the same ward is patient-to-patient transmission of the isolate, usually through the hands of staff, contaminated equipment, or the overall hospital environment [1,2,127]. It should be realized that available preventive measures are mainly derived from human studies. Given the rapid spread of MDR A. baumannii in clinical institutions, two different approaches are essential to limit the spread of antimicrobial-resistant A. baumannii, namely infection control and antimicrobial control programs. The first approach requires compliance with a series of methods including strict environmental cleaning, effective sterilization of reusable medical equipment, concentration on proper hand hygiene practices, and use of contact precautions, together with appropriate administrative guidance. The second strategy is also of paramount importance. Both are essential for control of antimicrobial-resistant A. baumannii spread and infections [16,125,128]. In line, it is critical for the veterinary community to engage in discussions pertaining to prudent and effective use of antimicrobials and to consider ways to improve antimicrobials use practices, to optimize animal care, reduce antimicrobial resistance selection pressure and maintain access to important antimicrobial agents. However, there are no simple solutions to this complex problem, yet veterinarians must consider the influence of the decisions that they make on a daily basis and optimize antimicrobial use for the benefit of their patients and society as a whole [129]. Furthermore, innovations associated with potent antibacterial efficacy against MDR isolates of A. baumannii should be mentioned here too. For instance light modulates the ability of A. baumannii to persist in the environment, its virulence against eukaryotic hosts, and even susceptibility to certain antimicrobials. The light signal is sensed through different mechanisms,
in some cases involving specialized photoreceptors of the BLUF-type, whereas in others directly by a photosensitizer molecule [130]. Continuous flow-through unit (45 J/cm²) UVC treatment of sterile, colostrum and commercial whole milk inoculated with A. baumannii caused a significant reduction of bacterial counts [131]. In addition, both maleic anhydride-based novel cationic polymers appended with amide side chains [49] and an electrochemical scaffold that generates a local low concentration of hydrogen peroxide [130] showed to disrupt surface established MDR A. baumannii biofilms. As a consequence, these innovations were associated with potent antibacterial efficacy against MDR A. baumannii with minimal toxicity to mammalian cells. Furthermore, newly isolated bacteriophages can serve as potential candidates for phage cocktails to control A. baumannii infections [132]. Nevertheless, antimicrobials remain to date the therapeutic option and it is therefore of major importance to use them appropriately after consultation of an antibiogram and in case of infections only.

There is an increase of awareness regarding antimicrobial stewardship in veterinary medicine [133]. Establishment of antimicrobial stewardship programs requires (1) coordination ideally by an infectious diseases specialist or at least by a clinician with strong interest in and good knowledge of antimicrobial resistance and therapy, (2) commitment by the clinical staff, and (3) collaboration with the microbiology laboratory.

Although the problems associated with healthcare-associated infections and the emergence of zoonotic and MDR pathogens in companion animal (dogs, cats and horses) medicine have been well-known for decades, current progress with respect to practical implementation of infection control programs in veterinary clinics has been limited [134]. Significantly reducing transmission of infections in small animal veterinary clinics, as in human hospitals, will require “clear goals, a committed leadership, access to resources, a best-practice mindset, effective people management, and ongoing vigilance” [135]. However, this field needs more awareness in veterinary medicine. For instance, about half the small animal practitioners and less than a
third of the large animal or equine practitioners reported always washing their hands before eating, drinking or smoking. The frequency of hand washing between contacts with patients was even lower [136,137]. Increasing concerns about zoonoses and antimicrobial resistance are bringing public health and private veterinary practice together. An emphasis on prevention will pay rich dividends for the safety of our patients and staff and the broader community [137].

10. Public Health Significance

Most _A. baumannii_ infections in humans involve the respiratory tract, but bacteremia, meningitis, UTI, (prosthetic) valve endocarditis, endophthalmitis, keratitis and wound/soft tissue infection may also occur [10,16,124], especially in ICUs [1,138]. Community-acquired _A. baumannii_ is a rare, but serious cause of community-acquired pneumonia in tropical regions of the world. These infections predominantly affect individuals with risk factors, which include excess alcohol consumption, diabetes mellitus, smoking, and chronic lung disease. Community-acquired _A. baumannii_ pneumonia presents a surprisingly fulminant course and is characterized by a rapid onset of fever, severe respiratory symptoms, necrotising fasciitis and multi-organ dysfunction, with a mortality rate reported as high as 64% [16,139-143].

The rapid spread of MDR _A. baumannii_ in clinical institutions has made choosing an adequate antimicrobial to treat these infections and executing contact precaution to isolate these MDR _A. baumannii_ difficult for clinicians [125,128].

Since animals may represent a reservoir for _A. baumannii_, it is of public health importance to avoid selecting MDR strains through the uncontrolled application of clinically essential antimicrobials.

Conclusions
A. baumannii represents nowadays an important veterinary nosocomial pathogen. However, it seems that the majority of A. baumannii infections in veterinary medicine are secondary and as a sequela might be fatal or lead to euthanasia in some cases. The recent report on A. baumannii infection in farmed mink might be regarded as an exception with reference to the associated fatal pneumonia. In other species relevant to veterinary medicine fatal pneumonia as a sequela of A. baumannii infection seems rare. Emergence of cases of infections in companion animals associated with carbapenem-resistant isolates emphasizes the need for accurate diagnostics. Treatment of diseased animals is often supportive and specific treatment should be based preferably on in vitro ASTs. Although the role of animals is still not clear in the dissemination of specific clones into the human community and hospitals, studies have demonstrated that similar or even identical A. baumannii clones have been identified in both settings. However, this finding is limited to hospitalized animals with nosocomial infections. It is therefore of major importance to avoid the selection and spread of MDR A. baumannii in animals as it is in humans, use targeted antimicrobial therapy as well as implement infection control. Among effective control procedures of antimicrobial-resistant A. baumannii infections in veterinary hospitals in our experience concentration on proper hand hygiene practices is the key.

**Declarations**

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**Competing Interests:** None declared

**Ethical Approval:** Not required

**Authors’ contributions**
JHvdK initiated and coordinated the review. JHvdK drafted the manuscript and VG, AE, CG and VP participated in the design and editing of the manuscript. All of the authors read and approved the final manuscript.
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Table 1. Overview of methodologies used for the identification of *Acinetobacter* isolated from animals.

<table>
<thead>
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<th>Animal (n)</th>
<th>Infection site</th>
<th>Identification method</th>
<th>Reference method</th>
<th>Species identification at time of publication</th>
<th>Reliable identification</th>
<th>Year of publication</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
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<td>NM</td>
<td><em>rpoB</em> sequencing</td>
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<td>Dog (n=168)</td>
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<td><em>gyrB</em> multiple x PCR</td>
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<td>Gingival scrapings from healthy dogs</td>
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<td>2007 92</td>
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NM = not mentioned
Table 2. Transmissible antibiotic resistance genes identified in carbapenemase-containing *Acinetobacter* species from animals

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