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Treatment of infections caused by multi-resistant microorganisms in hospital at home units

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ABSTRACT

Hospital at home units allow the treatment of moderate and severe infections by administering intravenous antibiotics to patients who would otherwise have to remain hospitalised. Increasing antibiotic resistance adds an element of difficulty to outpatient treatment of infections because multiple daily doses of antimicrobials or combinations of antimicrobials are sometimes required. This manuscript discusses some of the challenges of outpatient management of infections with multidrug-resistant microorganisms and shows the main antibiotic resistances and the outcomes of treatment of these infections in Spanish home hospitalisation units.

Keywords: multidrug-resistant microorganisms, hospital at home, OPAT, intravenous antibiotic treatment.

Infections caused by multi-resistant microorganisms represent a challenge for healthcare organisations, not only because of the risk to patients, but also because of the consumption of resources. In hospitals, multidrug-resistant infections force beds to become unusable to ensure isolation measures, and the frequent need to treat these infections with intravenous antibiotics results in prolonged hospital stays.

Outpatient treatment of these infections can help relieve hospital pressure and, in turn, reduce the risk of nosocomial infections. However, treating infections caused by multidrug-resistant microorganisms at home presents a new challenge. The lack of room temperature stability of some antimicrobials that are administered several times a day intravenously or the need to combine antibiotics to broaden the spectrum or achieve synergies can make home therapy difficult.

For this reason, the choice of antibiotic for outpatient treatment is sometimes made on the basis of ease of administration regardless of clinical practice guidelines and recommendations. In one study, outpatient therapy with antibiotics administered as a single daily dose was found to be inadequate in 28% of patients [1]. Therefore, the choice of antimicrobial should not be based on the ease of administration of the drug, as this may lead to further resistance or therapeutic failure; this decision should rather be based on its activity, efficacy and safety profile.

The appropriateness of the use of parenteral antibiotics in the outpatient setting is related to the organisation, resources and competence of the team treating and monitoring patients with infectious conditions. These circumstances may also influence treatment outcomes. Salles *et al.* observed that a lack of medical visits was a predictor of readmission and mortality for patients receiving outpatient antimicrobial therapy [2].

The home hospitalisation model is staffed by healthcare professionals with hospital dependency and training who monitor and control patients on a daily basis. This model allows early identification of complications and control of the evolution of the infectious process, and may explain why the therapeutic success rate is over 90% and the return rate to hospital is less than 8% in large series of cases [3]. Even so, the risk of treatment inadequacy remains [4].

Regardless of the care model, outpatient parenteral antimicrobial therapy cannot be considered as an isolated procedure, but as an organised process that includes criteria for the selection of patient, drug, venous access route and infusion modality, daily monitoring of infection evolution, indication and interpretation of complementary tests, de-escalation and sequencing of antibiotics when indicated, duration of treatment, discharge planning and subsequent follow-up [5]. The need to ensure safe and effective outcomes has recently prompted the development of quality indicators for the practice of outpatient parenteral antimicrobial therapy [6].

In addition, in the case of multidrug-resistant microor-

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Table 1 Microbiological isolates (all samples) and antibiotic resistance in Spanish home hospitalisation units (source: TADE Registry)

Microorganism	Total isolates	Isolates with antibiotic resistance, n (%)					
		Amoxicillin-clavulanate	Ampicillin	Ceftriaxone	Ciprofloxacin	Ertapenem	Gentamicin
Escherichia coli	2,657	932 (35.1)	1710 (64.4)	856 (32.2)	1325 (49.9)	18 (0.7)	479 (18.0)
Proteus mirabilis	229	67 (29.3)	122 (53.3)	47 (20.5)	116 (50.7)	11 (4.8)	60 (26.2)
Klebsiella pneumoniae	685	327 (47.7)	518(75.6)	347 (50.7)	373 (54.5)	29 (4.2)	190 (27.7)
Enterobacter cloacae	168	135 (80.4)	124 (73.8)	72 (42.9)	55 (32.7)	6 (3.6)	27 (16.1)
		Amikacin	Ceftazidime	Ciprofloxacin	Gentamicin	Imipenem-cilastatin	Piperacillin-tazobactam
Pseudomonas aeruginosa	1650	144 (8.7)	307 (18.6)	951 (57.6)	519 (31.5)	426 (25.8)	342 (20.7)
		Ciprofloxacin	Cloxacillin	Trimethoprim-sulfamethoxazole	Daptomycin	Penicillin	Vancomycin
Staphylococcus aureus	559	138 (24.7)	171 (30.6)	30 (5.4)	8 (1.4)	361 (64.6)	18 (3.2)
Staphylococcus epidermidis	177	92 (52.0)	103 (58.2)	71 (40.1)	3 (1.7)	108 (61.0)	6 (3.4)
		Ampicillin	Daptomycin	Gentamicin	Linezolid	Penicillin	Vancomycin
Enterococcus faecalis	328	15 (4.6)	6 (1.8)	83 (25.3)	3 (0.9)	20 (6.1)	3 (0.9)

ganisms, the choice of antimicrobials should take into account risk factors for resistance. Carrier states, high local incidence, recent hospitalisation, recent and repeated use of antibiotics, instrumental manipulations and health care are all risk factors for antibiotic resistance. For each microorganism there are, in addition, some specific risk factors [7,8].

One aspect not yet fully resolved is the stability of some antimicrobials at room temperature. This property of drugs is crucial as lack of stability limits the home use of antibiotics that are administered more than once a day. When nursing shifts allow, antimicrobials can be administered every 12 hours, even if they are not stable. For the rest, the solution is refrigeration in a refrigerator and self-administration, or infusion via systems that allow the dilution to be kept refrigerated. The latter is not sufficiently widespread and has the disadvantage of the need to incorporate a temperature control system and direct infusion of a cold dilution into the vein, which can be uncomfortable for the patient.

Meropenem is an example of an antibiotic for which there is a discrepancy between laboratory stability and clinical use. While most sources do not give this drug a room temperature stability of more than 12 hours at different concentrations and with different diluents, some authors have successfully used it in continuous infusion without refrigeration [9,10].

For drugs that are not stable at room temperature for 24 hours, self-administration of antibiotics intravenously is a safe procedure. It requires that the patient or caregiver is trained, properly instructed and supervised by health care personnel [11,12]. Today, self-administration is used even for stable drugs or antibiotics administered as a single daily dose.

Another aspect that has not been sufficiently analysed in outpatient antimicrobial therapy is the application of PK/PD principles [13]. In the presence of microorganisms with high MIC, the same recommendations should be followed as for any other patient, as well as for cases where the spectrum of activity or synergistic effect needs to be broadened by combining drugs. However, the benefit of strategies such as extended or continuous infusion of antibiotics in patients in the defervesce stage of infection, as in many of the patients seen in hospital at home, is less clear. Therefore, these strategies, and their efficacy compared to intermittent infusion in the outpatient setting, require further study to recommend their use [14].

Despite the rise of multidrug-resistant infections and the increasing activity of outpatient parenteral therapy, there are still few studies that specifically analyse the results of this practice in this type of infections. However, the available data suggest that the efficacy of treatment, both in targeted and empirical therapy, is comparable to those caused by sensitive microorganisms.

The registry of intravenous home antimicrobial therapy (TADE Registry) records infection treatment activity in Spanish home hospitalisation units. From July 2011 to December 2020, more than 12,000 episodes of infections treated at home were included. The registry analyses the microorganisms causing the infection and the pattern of antibiotic sensitivity of some of them to the main groups of antibiotics. Table 1 shows the main Gram-positive and Gram-negative microorganisms causing infections and the proportion of resistance to various antibiotics. Table 2 shows the percentage of cure or improvement of infections for each of them and the 30-day hospital readmission rate.

Table 2 **Cure/improvement and 30-day readmission[a] rates for microbiological isolates with antibiotic resistance (R) in home hospitalisation (source: TADE Registry).**

Microorganism	Outcome	Antibiotic resistance (R)					
		Amoxicillin-clavulanate R	Ampicillin R	Ceftriaxone R	Ciprofloxacin R	Ertapenem R	Gentamicin R
Escherichia coli	Cure/improvement	94.1%	95.2%	94.3%	94.4%	86.7%	94.1%
	30-day readmission	8.7%	6.4%	9.0%	7.7%	5.56%	6.5%
Proteus mirabilis	Cure/improvement	91.9%	93.0%	93.0%	91.9%	77.8%	91.2%
	30-day readmission	13.4%	10.7%	14.9%	11.2%	18.2%	15.0%
Klebsiella pneumoniae	Cure/improvement	92.6%	93.4%	91.8%	92.0%	85.2%	94.4%
	30-day readmission	8.9%	8.5%	10.1%	8.3%	0.0%	6.8%
Enterobacter cloacae	Cure/improvement	90.6%	91.5%	93.0%	88.9%	100.0%	92.6%
	30-day readmission	5.9%	5.6%	8.3%	7.3%	16.7%	11.1%
		Amikacin R	Ceftazidime R	Ciprofloxacin R	Gentamicin R	Imipenem-cilastatin R	Piperacillin-tazobactam R
Pseudomonas aeruginosa	Cure/improvement	87.2%	84.2%	88.4%	88.8%	88.1%	83.7%
	30-day readmission	16.0%	14.3%	11.6%	11.6%	13.1%	14.9%
		Ciprofloxacin R	Cloxacillin R	Trimethoprim-sulfamethoxazole R	Daptomycin R	Penicillin R	Vancomycin R
Staphylococcus aureus	Cure/improvement	91.5%	86.8%	85.7%	100.0%	90.4%	93.3%
	30-day readmission	9.4%	7.6%	16.7%	0.0%	8.3%	5.6%
Staphylococcus epidermidis	Cure/improvement	84.9%	87.2%	81.8%	66.7%	86.7%	80.0%
	30-day readmission	6.5%	3.9%	4.2%	33.3%	3.7%	16.7%
		Ampicillin R	Daptomycin R	Gentamicin R	Linezolid R	Penicillin R	Vancomycin R
Enterococcus faecalis	Cure/improvement	85.7%	75.0%	89.5%	100.0%	80.0%	50.0%
	30-day readmission	20.0%	0.0%	9.6%	0.0%	5.0%	33.3%

[a]Relative to the total number of isolates with resistance to each antibiotic

These data suggest that treatment of infections caused by multidrug-resistant microorganisms in hospital at home is common and effective, although with differences depending on the microorganism and the antibiotic(s) to which it is resistant. The organisation of these units with doctors and nurses following up patients on a daily basis may explain these good results. However, more information is needed on the appropriateness of antimicrobial treatment to clinical practice guidelines and recommendations in the home setting.

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CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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