# Management of healthcare-associated infections at the end of life – a cross-sectional study

## *Postępowanie w zakażeniach związanych z opieką zdrowotną u kresu życia – badanie przekrojowe*

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## Abstract

A retrospective chart review was performed on 1458 patients admitted to the free-standing hospice between 1 September 2013 and 31 January 2016. A total of 134 (9.2%) patients (123 with advanced cancer) were clinically diagnosed with 172 cases of various healthcare-associated infections (HAI): two, three, and four times in 26, 5, and 1 person/s, respectively. The median length of care within the infected group was 32.0 days (vs. 9.6 days for non-infected). The most prominent infection risk factors identified were prolonged steroid therapy (37.0% of episodes), antibiotics used before the admission (23.7%), and bladder catheterisation (23.9%). The most common types of HAI were lower respiratory tract infection (LRTI; 43.0%), end-of-life infection of unknown origin (EOL-IUO), urinary tract infection (UTI) (17.4% each), and Clostridium difficile-associated diarrhoea (9.9%). Antibiotics most often used were gentamicin (once-only dosage) in EOL-PUO (27.9% of episodes), ceftriaxone in LRTI (17.4%), and levofloxacin in UTI (15.7%). In 18.0% of cases a sequence of two antibiotics was required. In 4.0% of episodes a sole symptomatic therapy was continued. Clinically meaningful improvement after the full course of antimicrobials was achieved in 79.5% of cases. Once-only antimicrobial was still efficacious but less so (52.1%, $p = 0.0006$) and comparable with sole symptomatic treatment ($p = 0.7$). The cost of antibiotics was 16.7% of all drug expenses. Antibiotic therapy appeared to be a frequently chosen, effective although expensive symptomatic management at the end of life.

**Key words:** infections, antimicrobials, palliative care.

## Streszczenie

Dokonano retrospektywnej oceny dokumentacji medycznej 1458 pacjentów przyjętych do wolno stojącego hospicjum pomiędzy 1 września 2013 a 31 stycznia 2016 r. U 134 (9,2%) osób, w tym 123 z nowotworem złośliwym, stwierdzono 172 przypadki rozpoznania zakażenia związanego z opieką zdrowotną (w tym dwukrotnie u 26 chorych, trzykrotnie u pięciu i czterokrotnie u jednej osoby). Mediana czasu opieki nad chorymi z infekcją wyniosła 32 dni (9,6 dnia u pozostałych bez stwierdzonej infekcji). Najczęstszymi stwierdzonymi czynnikami ryzyka były przewlekła steroidoterapia (37,0% epizodów), uprzednio stosowana antybiotykoterapia (23,7%) oraz cewnikowanie pęcherza moczowego (23,9%). Do najczęstszych typów infekcji należały zakażenia dolnych dróg oddechowych (43,0%), infekcje ostatnich dni życia, zakażenie dróg moczowych (po 17,4%) oraz biegunka związana z zakażeniem *Clostridium difficile* (9,9%). Najczęściej stosowanymi antybiotykami były gentamycyna w jednorazowej dawce, stosowana w infekcji ostatnich dni (27,9% przypadków), ceftriakson w infekcjach oddechowych (17,4%) oraz lewofloksacyna w zakażeniu dróg moczowych (15,7%). W 18,0% przypadków stosowano sekwencję dwóch antybiotyków, a w 4,0% jedynie leczenie objawowe. Istotną klinicznie poprawę uzyskano w 79,5% przypadków zastosowania pełnego leczenia antybiotykiem. Podanie jednorazowe antybiotyku okazało się skuteczne, ale w mniejszym stopniu (52,1%, $p = 0,0006$) i porównywalne z postępowaniem jedynie objawowym ($p = 0,7$). Koszt stosowania antybiotyków wyniósł 16,7% całkowitych wydatków lekowych. Antybiotykoterapia okazała się skutecznym, lecz kosztownym, często wybieranym sposobem leczenia u kresu życia.

**Słowa kluczowe:** infekcje, antybiotyki, opieka paliatywna.

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## INTRODUCTION

Clinical signs of infection accompany nearly one third of advanced-disease patients [1]. The majority (53.0%) of patients on palliative care consultation receive empiric antibiotics [2]. Even after transition to comfort care, more than one third of patients may remain on antimicrobials [3]. Lack of clear hospice guidelines regarding antibiotic use may lead to a growing number of patients receiving potentially unnecessary or potentially burdensome treatment for infection [4]. Antibiotic treatment of these common diagnoses remains a challenge due to difficulties in predicting the individual therapeutic outcomes [5]. The objective of the current study summarising the institutional infection control team (ICT) activity was to determine the prevalence of healthcare-associated infections (HAI), the therapeutic strategies used, and their outcomes within hospice patients.

## METHODS

The medical records of all consecutive patients (Gold Standards Framework stage C-D [6]) admitted to the hospice acute 42-bed ward in a metropolitan city of 780 thousand inhabitants between 1 September 2013 and 31 January 2016 were reviewed. Information on any potential infection risk factors was obtained from patients' records on admission. The presence of symptoms and signs assessed to have been caused by microbial agents according to revised McGeer Criteria [7] allowed us to categorise patients into a infected patients group (IG) and a non-infected group (NIG). Episodes of infection that occurred within two days following the admission or mucosal thrush were not taken into account and excluded. Infection suspicion of unexplained origin (with fever ≥ 2 times within 12 hours) [8] in moribund patients were classified as end-of-life infection of unknown origin (EOL-IUO). The clinical outcomes within the IG were classified into: "clinical cure" (when all constitutional symptoms and signs of infection ceased), "symptomatic relief" (all symptoms disappeared but signs persisted), "symptomatic alleviation" (some symptoms disappeared or diminished), "symptomatic stabilisation", and "worsening". The comparison of antibiotics costs with all drugs expenses was made.

Fisher's exact test was used to compare categorical data, the Wilcoxon rank sum test was used to compare ordinal data between the analysed groups. Kruskal-Wallis test was performed to assess the results in various types of infection. A $p$ value of 0.05 was considered statistically significant. Institutional approval for this retrospective study was obtained.

## RESULTS

Ninety per cent of 1458 admitted patients had cancer, 70.0% were totally bed-bound, and nearly half of them were hospitalized within six months before the admission (on average twice; range 1–13). The characteristics of admitted patients within the IG and NIG subgroups are presented in Table 1.

In total, 134 patients in IG (9.2%) were diagnosed with various types of HAI. They had an average of 3.51 infection risk factors (compared with 3.75 in NIG; $p = 0.1$). Patients with more than one infection episode per admission had an average of 4.38 (range 2–9) risk factors, compared with 3.28 (range 1–8; $p = 0.0048$). Patients in IG more often received antibiotics in the six months prior to the admission. The

**Table 1.** The characteristics of admitted patients within IG and NIG

| Characteristics | IG *n* = 134 | | NIG *n* = 1324 | | *p* | |
|---|---|---|---|---|---|---|
| Median days of care (IQR) | 32.0 | (11–100) | 9.6 | (3–24) | < 0.0001 | b |
| Median days of care after infection (IQR) | 12.0 | (3–32) | – | | | |
| Mean age, years (SD) | 70.2 | (12.6) | 68.2 | (11.8) | 0.8 | b |
| Females | 69 | 51.5% | 698 | 52.7% | 0.9 | a |
| Palliative Performance Scale ≤ 40 points | 95 | 70.9% | 927 | 70.0% | 0.9 | a |
| Died at the hospice | 126 | 94.0% | 1250 | 94.4% | 0.8 | a |
| Primary cancer | 122 | 91.0% | 1177 | 88.9% | 0.6 | a |
| Genitourinary | 42 | 31.3% | 420 | 31.7% | 0.7 | a |
| Digestive tract | 34 | 25.4% | 337 | 25.5% | 0.7 | a |
| Lung | 32 | 23.9% | 298 | 22.5% | 0.8 | a |
| Brain | 7 | 5.2% | 56 | 4.2% | 0.7 | a |
| Other neoplasms | 7 | 5.2% | 89 | 6.7% | 0.3 | a |
| Non-malignant disease | 12 | 9.0% | 124 | 9.4% | 0.9 | a |

*QR – interquartile range (25.0–75.0%); SD – standard deviation; a – Fisher's exact test; b – Wilcoxon rank sum test*

**Table 2.** Infection risk factors within IG and NIG patients on admission

| Risk factor | IG | | NIG | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Hospitalisation within 6 months prior to admission | 62 | 46.3 | 627 | 47.4 | 0.8 |
| Prolonged steroid therapy (> 2 weeks) | 48 | 35.8 | 334 | 25.2 | 0.009 |
| Antibiotics within 6 months prior to admission | 36 | 26.9 | 224 | 16.9 | 0.006 |
| Bladder catheter | 32 | 23.9 | 276 | 20.8 | 0.04 |
| Diabetes | 21 | 15.7 | 146 | 11.0 | 0.1 |
| Radiotherapy within 6 months | 15 | 11.2 | 174 | 13.1 | 0.6 |
| Congestive heart failure | 14 | 10.4 | 117 | 8.8 | 0.5 |
| Chemotherapy within 6 months | 13 | 9.7 | 176 | 13.3 | 0.3 |
| Renal insufficiency | 8 | 6.0 | 27 | 2.0 | 0.01 |
| Other catheters | 7 | 5.2 | 98 | 7.4 | 0.5 |
| Hepatic insufficiency | 5 | 3.7 | 61 | 4.6 | 0.8 |

*P-values calculated using Fisher's exact test*

**Table 3.** Types of diagnosed HAI within IG

| Type of infection | n | % |
|---|---|---|
| LRTI | 76 | 44.2 |
| UTI | 30 | 17.4 |
| EOL-IUO | 30 | 17.4 |
| CD – associated diarrhoea | 17 | 9.9 |
| Skin infection | 13 | 7.6 |
| Suspected infectious diarrhoea | 4 | 2.3 |
| Purulent conjunctivitis | 2 | 1.2 |
| Total | 172 | 100.0 |

*EOL-IUO – end-of-life infection of unknown origin; UTI – urinary tract infection; LRTI – lower respiratory tract infection*

prevalence of renal insufficiency, prolonged steroid therapy, and bladder catheterisation within this group was higher (Table 2).

Thirty-two patients had more than one HAI episode (2, 3, and 4 times in 26, 5, and 1 person/s, respectively). The most common types of HAI were lower respiratory tract infection (LRTI) in 44.2% of episodes, and less prevalent were EOL-IUO and urinary tract infection (UTI; 17.4% each). In 17 cases (out of 21 diarrhoeas associated with antibiotics) *Clostridium difficile* (CD) aetiology was confirmed – three times as a consequence of antibiotics given at the hospice (Table 3).

A full course antibiotics was used 135 times in 117 HAIs (two drugs given in 18 cases) among which intravenous ceftriaxone applied in LRTI (30 times) or levofloxacin in UTIs (27 times) were the most common. According to physician's preference, a single dose of gentamicin was chosen in 48 cases (23 EOL-IUOs, 12 lower respiratory tract infections and six UTIs) – sole symptomatic management was given in seven cases of EOL-IUOs. Twenty-three positive microbiology results were obtained: 14 CD toxins in faeces and nine various species in urines (*Proteus mirabilis* – three; *Escherichia coli* – two; meticillin-resistant *Staphylococcus aureus* (MRSA) – one, and acquired resistance to macrolides, lincosamides, and streptogramin B *Staphylococcus aureus* (MLS) – one; *Enterococcus faecalis* – one; *Pseudomonas aeruginosa* – one, and mixed species – one case). The pathogen-directed therapy covered 23 (13.2%) HAIs, predominantly with 14 days of oral metronidazole or vancomycin for post-antibiotic diarrhoea. Clinical improvement was seen in 121 cases (70.3%) and symptom aggravation in eight cases (4.7%) for whom the infection was fatal (Table 4).

**Table 4.** The comparison of the treatment effects within IG subgroups: 10–14-day course of antibiotics (antib > 1x), gentamicin single dose (genta 1x), and with no antibiotics (no antib)

| Effect | antib > 1x | | genta 1x | | no antib | | total episodes | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Clinical cure | 37 | 31.6 | 0 | 0.0 | 0 | 0.0 | 37 | 21.5 |
| Symptomatic relief | 39 | 33.4 | 9 | 18.8 | 2 | 28.5 | 50 | 29.1 |
| Symptomatic alleviation | 17 | 14.5 | 16 | 33.3 | 1 | 14.3 | 34 | 19.7 |
| Symptomatic stabilisation | 22 | 18.8 | 19 | 39.6 | 2 | 28.6 | 43 | 25.0 |
| Symptomatic worsening | 2 | 1.7 | 4 | 8.3 | 2 | 28.6 | 8 | 4.7 |
| Total | 117 | 100.0 | 48 | 100.0 | 7 | 100.0 | 172 | 100.0 |

In the full course of antibiotic therapies a significant symptomatic improvement was noted, which was more effective than the single-dose gentamicin (79.5 vs. 52.1%; $p = 0.0006$) or sole symptomatic management (42.9%; $p = 0.045$). The cost of antibiotics was 16.7% of all drug expenses (the second position behind analgesics) – for 10.2% of all admitted patients.

## DISCUSSION

The ICT activity could explain the quite low (9.2% of patients) prevalence of infections observed in this study, lower than the 18.7% seen in nursing homes. It was possible through a strict sanitary regime, infection surveillance, limiting exposure (e.g. avoidance of unnecessary bladder catheterisation [9]), and monitoring asymptomatic infections, which can be found particularly in this group of patients [10]. However, other hospice studies noticed that up to 42% of terminally ill patients developed infections in the final phase of care, with one-fifth being fatal [11, 12]. The incidence rate of infections in our group (0.59% of care days) was twice as high as that observed in long-care term facilities (LCTF; 0.27% of care days), probably due to shorter length of stay [10]. In our observation infection diagnoses were associated with longer time of care, suggesting unfavourable length of stay influencing infection risk rather than an increased survival due to the use of antimicrobials. The literature gives inconsistent data in this area [13–15].

The evident number of infection risk factors within the end of life, the majority among bed-bound cancer patients, did not clearly increase this risk in IG (all admitted patients had a marked hazard of infection), as was observed in the literature [16]. It did not correspond with the increased relative risk (RR; 1.2–3.1) of pneumonias in more debilitated, with limited activity, poor nutritional status, catheterised, and tube-fed patients within LTCFs [17]. A higher mean number of risk factors within the patient subgroup of multiple infections was noted. Three modified risk factors were observed (antibiotics, prolonged steroids, and bladder catheterisation), which suggests room for prevalence improvement [18].

In our study LRTIs occurred most commonly, twice as often as UTIs, as opposed to more prevalent UTIs in some observations [12]. Antibiotic-associated diarrhoea (predominantly of CD origin) was the third leading cause, usually due to hospital antibiotics before the admission. Approximately half of those admitted came directly from hospitals, including intensive care units. In only three cases was this complication the sequence of antibiotics used at our hospice, increasing the costs of care [19, 20].

General avoidance of specimen culture testing (e.g. urine by catheterisation) was the dominant principle on the ward. A twice-daily routine of patient's temperature monitoring was the main infection screening tool at the hospice. Approximately two thirds of the fever episodes can be due to infection, primarily of bacterial origin (usually respiratory infections due to Gram-negative bacilli) [21]. In nearly one fifth of cases within the last days of life pyrexia can be the only infection indicator. There are consistent findings indicating that treating residents for bacteriuria without symptoms is not beneficial, and possibly harmful [22]. Suspicion of bacterial diarrhoea led to the performance of toxin tests. Besides CD, multi-resistant species were revealed that can have a significant impact on advanced cancer patients and their families [23].

There are no generally accepted guidelines on antibiotic use at the end of life [24]. The antibiotic usage (8.7% of all admitted patients) was much lower than up to one third of all within the last week of life seen among patients admitted to long-term facilities or hospices [25–29]. The available studies suggest that educational interventions, including ICT activity, may reduce the number of antibiotic starts and also the days of therapy [30, 31].

Ninety per cent of infected patients in our population were treated by antimicrobials. When fever was added to the rapid (visible in terms of hours or days) multiorgan failure process, patients received a single dose of aminoglycoside. Major concerns appeared in such end-of-life situations about the risk of futility, escalating the drug toxicity, or prolonging the dying process [32]. Occasionally the watchful waiting strategy and delayed antibiotic initiation ("two-day rule") [33] or Naproxen test (fever lysis in paraneoplastic syndrome) were tried in our hospice [34, 35]. End-of-life patients should receive antibiotics with the purpose of relieving symptoms, less commonly to eradicating infection or even to prolonging life [36]. Evident symptomatic improvement was achieved in 70.0% of all HAI cases (weakly negatively correlated with the number of risk factors), which is higher than noticed in the literature [12, 28, 36, 37]. A time-limited trial of antibiotics for some hospitalised advanced cancer patients may be reasonable because it may have comparable symptomatic effects to longer treatment. Even given once only, antimicrobials (gentamicin 160–240 mg or ceftriaxone 1–2 g) gave a substantial (40.0%) positive response rate in 15 out of 23 infected patients [38] or reduction of infective terminal respiratory secretions resistant to hyoscine [39]. This method often allowed postponement of the necessity of other symptomatic treatment usage, including antipyretics, antitussives, or analgesics.

## CONCLUSIONS

Antibiotic therapy appeared to be a frequently chosen, valuable, although expensive symptom-alleviating management at the end of life. Empirical antibiotic full-course therapy improved symptoms in four fifths of HAIs; single-dose aminoglycoside was less effective and comparable with sole symptomatic management.

*Authors report no conflict of interest.*

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