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ANTIMICROBIAL USE AND MICROBIOLOGICAL TESTING IN DISTRICT GENERAL HOSPITAL ICUs OF THE VENETO REGION OF NORTH-EAST ITALY

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ABSTRACT

Purpose. International - predominantly American - studies undertaken in the ICUs of teaching centres show that inadequate antibiotic therapy increases mortality and stay. We sought to ascertain whether this pertains also for smaller ICUs in the Veneto region of North-east Italy. To the best of our knowledge, this is the first such survey in the Veneto or in Italy as a whole.

Methods. A retrospective, observational study was performed across five general-hospital ICUs to examine appropriateness of microbiological sampling, empirical antibiotic adequacy and outcomes.

Results. Among 911 patients (mean age, 65.8 years ± 16.2 SD; median ICU stay, 17.0 days [IQR, 8.0-29.0]), 757 (83.1%) were given empirical antibiotics. Treatment adequacy could be fully assessed in only 212 patients (28.0%) who received empirical treatment and who had a relevant clinical sample collected at the initiation of this antibiotic (T0). Many other patients only had delayed microbiological investigation of their infections between Day 1 to Day 10 of therapy. Mortality was significantly higher among the 34.9% of patients receiving inadequate treatment (48.6% *vs*. 18.80%; $p < 0.001$). Only 32.5% of combination regimens comprised a broad-spectrum Gram-negative β-lactam plus an anti-MRSA agent, and many combinations were irrational.

Conclusions. Inadequate treatment was frequent and was strongly associated with mortality; moreover, there was delayed microbiological investigation of many infections, precluding appropriate treatment modification and de-escalation. Improvements in these aspects and in antibiotic stewardship are being sought.

KEYWORDS: ICU, microbiological sample, antibiotic, inadequate treatment.

INTRODUCTION

Patients admitted to intensive care units (ICUs) present challenging and complex clinical problems. The estimated risk for serious infection is 5 to 10 times greater than for patients on general medical wards owing to three major factors: (1) severe underlying disease, including multiple illnesses, malnutrition, extremes of age and immunosuppression; (2) invasive medical devices, such as endotracheal tubes for mechanical ventilation and intravascular and urinary catheters, which provide entry portals for pathogens; and (3) crowding, especially in neonatal ICUs, with consequent proximity to other colonized or infected patients, increasing the risk of cross-infection [1-3].

Antimicrobial resistance is a critical variable of ICU outcomes, co-determining patient morbidity, mortality and cost, at least in the major teaching centres where this topic has been largely investigated [4-12]. Kollef, in the U.S.A., found an infection-related mortality rate of 17.7% among 486 patients receiving appropriate empirical antimicrobial therapy versus 42% among 169 receiving inappropriate antimicrobial treatment ($p < 0.001$) [13]. The major single reason for antibiotic therapy being classed "inappropriate" was the presence of bacteria that had inherent or acquired resistance to the regimen. Others have found similar associations, particularly in bloodstream infections and sepsis [14-20], with mortality shown to increase progressively for each hour's delay in initiating adequate therapy after the onset of hypotension [21]. In the few countervailing studies, where an association between antibiotic resistance and mortality was *not* confirmed, few patients received microbiologically inappropriate therapy, due to early recognition of resistance and/or timely adjustment of the regimen(s) [22, 23]. Beyond its impact on mortality, initial inappropriate antibiotic therapy is also associated with extended length of stay for ICU patients [24-26].

It is less clear whether these relationships, demonstrated in teaching centres with a complex patient mix, hold true for the smaller ICUs of district general hospitals or in the context of different countries' cultures of prescribing and microbiological testing. We therefore present here the results of a multicentre, retrospective, observational study covering five ICUs in the Veneto region of North-east Italy, four of them in small hospitals and the fifth in a regional centre. The study had three main goals: first, to test whether, as elsewhere, there was a relationship between treatment

inadequacy and clinical outcomes; secondly, to examine the adequacy of first-line antimicrobial therapy prescribed and the principal reasons for any inadequacy; and, thirdly, to verify the appropriateness of microbiological testing performed in the participating ICUs.

PATIENTS AND METHODS

Study location and patients

The study was conducted from 2002 to 2010 at five general hospitals in the Veneto region of North-east Italy. Four hospitals were in small towns within 50 km of Vicenza and one in Vicenza itself, located between Venice and Verona. When this study was performed, the Vicenza hospital (Hospital 5) ICU had 14 beds, admitted approximately 700 patients per year, and was in a 1050-bed regional hospital; a further 5-bed high-dependency provision for post-surgical care was excluded. Hospital 1 (165 beds) admitted c. 350 patients per year to its 6-bed medical-surgical ICU; Hospital 2 (400 beds) had a 10-bed general ICU admitting c. 450 patients per year; Hospital 3 (350 beds) had a 6-bed general ICU admitting c. 240 patients per year; Hospital 4 (220 beds) had a 7-bedded ICU admitting c. 340 patients per year. The total number of ICU beds represented was 43, accounting for 10.8% of ICU provision in the Veneto and for 1.5% of 3739 Italy's total intensive care bed provision as of 2005 [27].

Data Collection

Patients admitted into the participating ICUs from 15 May 2002 to 10 June 2010 were assessed. Data input was performed manually in Microsoft Office Excel, with the following information recorded: hospital record number; gender; date of birth; date of hospital admission; date of ICU admission (if different); age at ICU admission, and main diagnosis at admission. Any other diagnoses indicated in the clinical records and constituting: (1) a co-morbidity, (2) a chronic disease directly related to ICU admission, or (3) a secondary pathological event that occurred during the

ICU stay was also recorded. For statistical analysis, diagnoses were classified into main categories, all as recognised in the WHO International Statistical Classification of Diseases and Related Health Problems [28]. The date of the primary outcome (death, or transfer to another unit) was recorded. Additionally, for patients transferred from the ICU to other units in the same hospital, the dates of transfer were recorded until the final outcome (death or discharge to home). The duration of ICU stay and entire hospital stay were calculated separately. For each antibiotic course, the regimen and dates of initiation and cessation were recorded. An antibiotic treatment was defined as empirical when it was initiated on the basis of a clinical suspicion of infection and when the causative microorganism and its antibiotic susceptibility were not yet known. Fungal infections were excluded. A sample was considered clinically relevant when it had been taken from a body site related to the reported infection.

Inadequate antimicrobial treatment was defined (based upon, e.g., [29,30) as the microbiological documentation of infection that was not being adequately treated at the time when the causative micro-organism and its antibiotic susceptibility became known, and included: (1) the absence of any agent directed against the family or genus of micro-organism present; (2) the administration of an antimicrobial agent to which the particular isolate was resistant; (3) the complete lack of antimicrobial treatment, and (4) the lack of adherence to minimum requirements in antibiotic administration (i.e., proper dosing, monitoring of drug levels when appropriate, and avoidance of unwanted drug interactions). A regimen was defined as adequate if it adequately covered all pathogens present in a sample taken at the time of clinical diagnosis (T0). Adequacy was considered not to be assessable if there was no T0 sample, if no pathogen was grown from a T0 sample, or if there was no concordance between the type of specimen sent to the laboratory and the patient's clinical presentation (e.g., clinically-diagnosed septic shock in post-surgical patients, but where the first isolates were grown from surgical wound swabs taken many days after initiation of empirical antibiotic treatment; or cases of sepsis where the only microbiological examinations performed were on bronchial aspirates). Cases where only questionable pathogens (principally

coagulase-negative staphylococci) were isolated were reviewed individually and discounted unless therapy was escalated on the basis of the microbiological result, implying that the organism was thought to be clinically significant.

Statistical analyses

Normally- or near-normally-distributed variables were reported as means with standard deviations and were compared by Student's t-test or by analysis of variance with the Bonferroni correction for multiple comparisons. Non-normally-distributed continuous data were reported as medians with interquartile ranges (IQRs) and were compared using the Mann-Whitney U-test or the Kruskal-Wallis test. The Spearman's *rho* correlation coefficient was calculated to measure the association at the ordinal level between mortality rates and their associated rates of inadequacy of first-line antimicrobial therapy. Kaplan-Meier methods were used to estimate survival rates during follow-up, whilst the log-rank test was used to test equality of survivor functions. Exploratory univariate analysis for several variables was performed to identify possible predictors of hospital mortality. Multivariable logistic regression analysis was conducted to investigate independent predictors for hospital mortality. Results of logistic regression analysis are reported as adjusted odds ratios (AORs) with 95% confidence intervals (CI). All statistical analyses were performed using STATA 10.1 (StataCorp LP, College Station, TX) and a two-sided $p < 0.05$ was routinely considered to be significant.

Ethics

The study was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Association, Helsinki, Finland, 1964 and later revisions [31]. Since it was performed retrospectively on specimens that were collected as part of the routine sampling required for the microbiological assessment of patients admitted into ICUs, there was no possible risk to any of the patients reviewed, nor any possible modification of their treatment. Consequently, individual consent was

not needed. The Institutional Sanitary Board of each hospital approved the protocol and confirmed that submission to their ethics committee was not required, provided that the principal investigator (PB) was personally responsible for the security of patient-identifiable data.

RESULTS

Patients

The study reviewed 911 patients admitted into the five ICUs (Table 1): 570 (62.6%) were men and 341 (37.4%) women. Eighty-eight (9.6%) had diabetes mellitus, 45 (5.0%) chronic renal failure, and 35 (3.9%) cirrhosis of the liver. Five hundred and fifty-two (60.6%) were admitted to an ICU with a medical diagnosis, 206 (22.6%) with a surgical diagnosis and 153 (16.8%) following major trauma. Their mean age upon ICU admission was 65.8 $\pm$ 16.2 years (range, 14 - 93); those admitted to the Hospital 5 ICU were significantly younger ($p < 0.001$) than those admitted elsewhere, partly reflecting a larger proportion of trauma patients. The median duration of ICU stay was 17.0 days (IQR, 8.0-29.0), with inter-hospitals difference approaching significance ($p=0.079$), while the median total length of hospital stay was 25.0 days (IQR, 14.0-44), with significant inter-centre variation ($p<0.001$).

Antibiotic treatment

A total of 3549 antimicrobial treatments were prescribed in the 5 ICUs over the study period. Of these, 3470 (97.8%) were parenteral and 79 (2.2%) oral. Seven hundred and fifty-seven patients (83.1%) received empiric antibiotic courses (1223 courses in total, 34.5% of all antimicrobial treatments) (Table 2). Monotherapy was used in 30.2% of empirical courses, with combination therapy used in 69.8%. The commonest empirical combinations were piperacillin/tazobactam plus a glycopeptide or linezolid (52 patients, 13.4%), a carbapenem plus a glycopeptide or linezolid (47 patients, 12.1%), a cephalosporin plus a glycopeptide or linezolid (27 patients, 7.0%),

piperacillin/tazobactam plus a fluoroquinolone (25 patients, 6.4%), a cephalosporin plus metronidazole (23 patients, 6.0%), and piperacillin/tazobactam plus metronidazole (21 patients, 5.4%).

Combination therapies included two antibiotics in 329 cases (85.0%), three in 55 cases (14.2%), and four in three cases (0.8%). Cephalosporins (148 courses) accounted for 40.1% of all empirical monotherapies, with cefazolin (first-generation) in 66 (44.6%), cefotetan (second-generation) in four (2.7%), cefotaxime, ceftazidime, and ceftriaxone (third-generation) in 69 (46.6%), and cefepime (fourth-generation) in nine (6.1%). Other frequently-prescribed monotherapies were piperacillin/tazobactam (74 courses, 20% of all monotherapies) and other penicillin/β-lactamase inhibitor combinations (68 courses, 18.4%).

Only 126 of the 388 combination regimens (32.5%) comprised a broad-spectrum Gram-negative β-lactam plus an anti-MRSA agent (a glycopeptide, usually teicoplanin, or linezolid); 91 (12.2%) of the first-line empirical regimens were irrational or redundant poly-pharmacy, commonly comprising a combination of a β-lactam with anti-anaerobe activity (i.e. a β-lactamase inhibitor combination or a carbapenem) with metronidazole.

The median duration of the first-line empirical therapy was 11.0 days (IQR, 6.7 – 19.0) for patients with bacteraemia, 9.0 days (5.0 – 14.0) for medical patients and 10.0 days (7.0 – 17.0) for surgical patients. Although there is a growing trend to shorten treatment durations, particularly in Northern Europe, these longer courses are typical of Italy in the study period and are not out of line with many international guidelines [32].

Laboratory data

There was often a poor match between the site of infection indicated in the patient record and the specimens from which organisms, if any, were grown by the laboratory. Moreover, there were

frequent long delays between the clinical diagnosis and any result becoming available to the treating clinician(s).

At the four smaller sites (Hospitals 1-4), respiratory samples accounted for >50% of all specimens with a pathogen grown, and for fully 74% and 82% at Hospitals 2 and 3, respectively (Figure 1). Blood and (especially) urine were rarely sampled, even when an infection was believed to involve these sites. Thus, at Hospitals 2 and 3, urines accounted for only 5.6% and 8.7% of total microbiological investigations, respectively. These patterns seem to reflect a practice of performing surveillance cultures of respiratory secretions and basing therapy upon these, rather than of undertaking microbiological investigations of actual infections.

Clinical specimens yielding an organism were collected at the initiation of empirical antibiotic (T0) only from 251 of the 911 patients (27.6%). Sixteen of these 251 did not receive antibiotics, as they were considered to be colonised rather than infected (n=13) or died early (n=3), leaving 235 patients who had a T0 specimen and an assessable empirical antibiotic treatment. This total reduced to 212 after exclusion of 23 patients whose T0 sample was from a body site different to the infection recorded in the patient's notes. Samples yielding reported organisms were taken within 10 days of therapy initiation from a further 361 patients (39.6%) whilst, in the remaining 299 cases (32.8%), the interval between initiation of antibiotic therapy and the first sample with a reported organism was >10 days, or there was no relationship between the type of specimen from which any organism was grown and the patient's clinical setting (Table 3). The median interval between the initiation of empirical antibiotic therapy and the availability of a first (post-infection) antibiotic sensitivity result was 7 days (IQR, 3.0-14.0), with significant variation amongst the five sites ($p < 0.001$). The lag between arrival of a growth-yielding sample at the laboratory and the availability of the result varied between sites from 3 to 4.5 days, meaning that around half of this overall 7-day delay was between the clinical diagnosis of infection and the specimen being sent to the laboratory for microbiology. It follows that many of the patients were already receiving

antibiotics at the time the first culture was taken, potentially compromising pathogen recovery and meaning that many were nearing the end of their antibiotic course when any microbiological results became available.

The lack of a T0 organism may be because no specimen was sent to the laboratory, or because no organism was grown by the laboratory. Discriminating these scenarios in the hospital record systems proved difficult but, for a random sample of 23 patients lacking culture results, we could identify six who had a relevant-site T0 sample from which the laboratory failed to grow a pathogen, eight who had only a T1 to T10 specimen failing to yield growth, and nine who had no evidence of any specimen being sent to the microbiology laboratory within 10 days of clinical diagnosis.

In total, 313 isolates from clinical samples (regardless of site and apparent relevance) were collected at T0 from the 235 patients starting empirical treatment. In 147 cases (62.6%) the organism(s) proved susceptible to the antibiotic regimen initiated whereas 88 (37.4%) patients had bacteria resistant to the regimen initiated. The lowest proportion of resistance was at Hospital 1 (25.0%) and the highest at Hospital 2 (42.4%). Resistance to the empirical therapy was more prevalent (192/347, 53%, $p < 0.001$) amongst cases who had initial isolates collected in the T1-10 period, again with the lowest proportion (49.1%) at Hospital 4 and the highest (61.5%) at Hospital 2. The differential in resistance, between patients with a T0 *vs*. T1-10 initial sample was moderately significant even in the bacteraemia subset, where 35/54 (64.8%) isolates from patients with a T1-10 sample were resistant to the empirical therapy given *vs*. 14/34 (41.2%) ($p = 0.098$) isolates from T0 samples, whilst the difference in resistance between the whole series bacteraemic *vs*. non bacteraemic patients was not significant ($p=0.1891$) (Table 4). Among the 212 patients who had clinically relevant T0 samples, resistance to the empirical therapy given was observed in 74 (34.9%), with the lowest proportion (22.6%) at Hospital 1 and the highest (40.6%) at Hospital 2 ($p = 0.2277$). A greater proportion of resistance to empirical therapy (142/266, 53.4%, was seen in cases with an initial T1-

10 sample, with the lowest rate (43.4%) at Hospital 4 and the highest (70.0%), again, at Hospital 2 (p=0.01). Amongst bacteraemic cases, 6/24 (25.0%) of T0 isolates were resistant compared with 13/25 (52%) among those collected from T1-10. There was little obvious demographic difference between the groups with a first relevant-site sample at T0, T1-10 and T>10 (or no relevant sample at all), with average ages of 66.3, 65.8, and 66.5 years and medical:surgical:trauma ratios of 73.5:15.5:11.0; 59.0:19.9:21.1 and 71.2:14.8:14.0, respectively.

The frequent lateness of microbiological data may explain the small proportion of cases (282 out of 757, 37.2%) in whom empirical regimens were adjusted based upon susceptibility results. The vast majority of these changes (252/282, 89.4%) were escalations, meaning the addition of further agents or switches to broader-spectrum agents; first-line empirical antibiotic was stepped-down in only 30 cases (10.6%).

Outcomes

Two hundred and twenty-seven patients (24.9%) died during their ICU stay and 316 (34.7%) during their entire hospitalization. One hundred and forty-three of the ICU deaths (63% of all ICU deaths) could reasonably be related to infection.

Patient primary outcome data in relation to treatment adequacy for the 212 cases with a relevant-site T0 clinical specimen is displayed in Table 5. Among the 74 (34.9%) whose empirical antibiotic(s) failed to cover the organisms subsequently identified there were 36 ICU deaths (48.6%) *vs*. 26 deaths (18.8%) among the 138 receiving therapy that covered all pathogens present (p <0.001). This pattern was maintained among patients whose first relevant specimen was taken in the T1-10 interval, where there was 43% mortality among those receiving inadequate therapy *vs*. 23% among those receiving adequate antimicrobial therapy (OR = 1.84; 95% CI, 1.3 to 2.5). In this case, however, it is impossible to distinguish whether inadequacy was against the initial pathogen, its resistant progeny, or against a secondary invader. Overall mortality rates among

patient with a first relevant-site sample at T0, T1-10 and T>10 (or no relevant sample at all were 29.2%, 19.9 % and 27.6%, respectively.

The adequacy of the initial regimen did not significantly affect the duration of ICU stay (p = 0.93) (Figure 2) partly because survivors who were hospitalized for extended periods were balanced by cases who died early.

Development of septic shock was a significant predictor of mortality as was the patient's age (p <0.001). Non-survivors also were more likely to have had acute renal failure upon admission (p < 0.001). By contrast, those admitted because of traumatic shock were more likely to survive (p < 0.001), perhaps owing to a higher probability of receiving adequate antibiotic treatment, given to 36.6% of trauma patients *vs*. 30.9% of other patient categories.

The commonest pathogens isolated from bloodstream samples and their associated rates of inadequate antimicrobial treatment were *P. aeruginosa* (n = 23; 80% inadequacy), MRSA (n = 19; 80% inadequacy), and *E. coli* (n = 14; 77% inadequacy). The large number of MRSA is unsurprising: EARS-net data (http://www.ecdc.europa.eu) show that the MRSA rate among bloodstream *S. aureus* fluctuated between 33.2 and 39.4% through the study period.

Despite extensive cephalosporin use (above) only two cases of *Clostridium difficile* diarrhoea were recorded, though it should be cautioned that diarrhoeal patients were not routinely screened for this pathogen in the study period, leading to likely under-recording.

DISCUSSION

Studies of antibiotic inadequacy and its consequences in severely-ill patients have largely been undertaken in teaching centres [13-21, 33-35], particularly in the U.S.A. [13,15,17,33]. We investigated whether their general conclusion - that inadequate empirical therapy is associated with increased mortality – applied also for smaller centres in the Veneto.

Assessing treatment adequacy proved challenging, owing to the many patients in whom microbiology was carried out improperly or belatedly. Clinical specimens were collected at initiation of empirical antibiotics (T0) for only 31.0% (235/757) of patients starting an initial empirical antibiotic course, and only 28% (212) had a sample taken from the reported infection site. In rather more cases (347, 45.8%), initial samples were taken between T1-10 whilst, for 299 cases (39.5%), the interval to the first sample was >10 days, or there was no concordance between any laboratory specimen and the patient's clinical setting. Resistance to the initial antibiotic therapy was significantly more prevalent amongst T1-10 isolates than among those collected at T0, regardless of whether comparison was irrespective of body site (55.3 *vs*. 37.4%) or solely from isolates from the relevant site (53.4 *vs*. 34.9%). Similar patterns – with greater resistance in T1-10 *vs.* T0 samples - were seen for the subset of bacteraemia patients (64.1% *vs*. 41.1% for isolates from any body site and 52.0 *vs*. 25.0% amongst bloodstream isolates). Greater resistance rates among 'late' isolates may reflect selection of resistance in the original pathogen, or super-infection by more resistant organisms during therapy.

When only the 212 empirically treated patients with a relevant T0 sample were analysed (Table 5), 138 (65.1%) treatments were assessed as adequate, with 18.8% deaths in the ICU, versus 74 (34.9%) judged inadequate, with 48.6% deaths) (p=<0.001). Total mortality among these 212 patients with timely microbiological investigation was 29.2% compared with 27.6% among the patients who had very belated microbiological investigation (>10 days) or no investigation at all. These two groups were well matched in terms of average age and proportions of medical *vs.* surgical *vs.* trauma cases; the overall similarity in outcome may well reflect the fact that, even where microbiological investigation was performed, therapy was rarely changed. Mortality was lower (19.9%) among the patients who had a first relevant sample in the T0-10 period, but this group contained a higher proportion of trauma patients, who anyway tended to have better outcomes.

This study, covering five small ICUs in the Veneto, thus confirms a significant association between inadequate empirical antimicrobials and ICU mortality. *S. aureus* and resistant gram-negative bacteria were the pathogens most frequently associated with poor outcomes, also as seen elsewhere [14,15,17,21,33-35]. Furthermore, and in keeping with a recent meta-analysis [36], ICU infections following trauma had lower mortality, perhaps because most trauma patients are younger and have fewer co-morbidities. In contrast to several published studies [8,14,18,20,24-26], we found no relationship between treatment adequacy and duration of ICU stay, though this calculation may be confounded by how duration is counted for patients who die early.

The frequent lack of prompt microbiological investigation is the core finding of this study. In many cases clinicians' undertook seemed to depend upon surveillance sampling for bacterial colonization of the lower airways rather than direct microbiological investigation of the clinically-diagnosed infections, often with an excess of antibiotics. Such overtreatment seems widespread in Italy [37,38] and elsewhere [38,40].

Even when relevant specimens were collected, they often were collected late, meaning that the organisms grown may have been secondary colonists, and that susceptibility results only became available around the time when primary empirical treatment was ending, or even afterwards. This may explain the infrequency of treatment de-escalation based on laboratory results. Even Hospital 5 - where laboratory results were available earlier - was little exception and, in all but two cases, changes to initial empirical antibiotic treatment were escalations, not de-escalations.

In summary, despite its limitations (e.g., being retrospective, exclusion of fungal infections, and the difficulty of evaluating empirical therapy among patients whose microbiological investigation was inadequate), this study provided a clear picture of sub-optimal microbiological testing and antibiotic use in the five ICUs. There was frequent antibiotic misuse, inappropriate empirical treatment, and high variability in (generally overlong) treatment duration and a considerable need for the ICUs to improve specimen-taking and use of the microbiology laboratory.

Notably, the ICUs lacked local antibiotic practice guidelines, which represent one tool for clinicians to manage patient and stewardship needs. Clinicians should be aware that any transient clinical benefit achieved by overtreatment is counterbalanced by collateral damage and detriment to the community as a whole via increased selection pressure for resistance. These issues are becoming even more serious and urgent with the recent and extensive dissemination in Italy of *Klebsiella pneumoniae* with KPC carbapenemases [20,41,42]. Poorly directed antibiotic use may have helped to drive this dissemination, which saw the proportion of carbapenem-resistant bloodstream *K. pneumoniae* in Italy rise from 1-2% from 2006-9 to over 30% in 2013-14 (http://www.ecdc.europa.eu). Most of these isolates are, however, clonal [43] and it therefore seems likely that infection control failures are a greater issue, a view supported by the observation that near-identical strains of carbapenemase-producing *K. pneumoniae* were reduced in prevalence in Israel by improved infection control rather than stewardship changes. Carbapenemase-producing K. pneumoniae remain rare at the ICUs included here (5-8 isolates, hospital-wide, per annum from 2010-12 in Hospital 5, rising to 14 in 2013, 18 in 2014 and 34 in the first half of 2015) but are hugely more prevalent in a major teaching centre just 60 km away (data not shown).

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CONFLICTS OF INTEREST

DML: Advisory Boards or ad-hoc consultancy for Accelerate, Achaogen, Adenium, Allecra, AstraZeneca, Auspherix, Basilea, BioVersys, Centauri, Cubist, Cycle, Discuva, Meiji, Nordic, Pfizer, Roche, Shionogi, Tetraphase, VenatoRx, Wockhardt; paid lectures – AOP Orphan, AstraZeneca, Merck, Nordic, Pfizer; relevant shareholdings in Dechra, GSK, Merck, Perkin Elmer, Pfizer amounting to <10% of portfolio value; contract research for Achaogen, Allecra Antiinfectives, AstraZeneca, Cubist Pharmaceuticals, GlaxoSmithKline, Merck, Meiji Melinta, and Wockhardt Ltd. All other authors have none to declare.

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Table 1 Characteristics of the study patients

Site	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Total	p-value §
N° of pts.	184	172	136	171	248	911	
N° (%) of male patients	119 (64.7)	107 (62.2)	89 (65.4)	102 (59.7)	153 (61.7)	570 (62.6)	0.819
N° (%) of female patients	65 (35.3)	65 (37.8)	47 (34.6)	69 (40.3)	95 (38.3)	341 (37.4)	0.819
Mean age (years) ± SD	69.4 ± 14.5	69.3 ± 14.7	65.3 ± 15.9	69.0 ± 14.6	58.7 ± 17.4	65.8 ± 16.2	< 0.001 ***
Age range (years)	18 - 92	20 - 93	17 - 91	16 - 91	14 - 89	14 - 93	
Median length of ICU stay (days) (IQR)	15.0 (7.7-25.0)	19.0 (9.0-33.5)	18.0 (10.0-30.0)	20.0 (7.0-33.0)	16.0 (9.0-24.0)	17.0 (8.0-29.0)	0.079 *
Median length of hospital stay (IQR)	19.0 (11.5–32.5)	35.0 (18.5–56.0)	25.0 (14.0–44.0)	31.5 (16.0-50.0)	22.0 (12.0–37.5)	25.0 (14.0–44.0)	< 0.001 ***
N° (%) of ICU deaths	40 (21.7)	50 (29.0)	33 (24.3)	37 (21.7)	67 (27.0)	227 (24.9)	0.383
N° (%) of hospital deaths	54 (29.3)	70 (40.7)	43 (31.6)	55 (32.2)	94 (37.9)	316 (34.7)	0.1239
Diagnosis on admission:							
Medical (%)	129 (70.1)	103 (59.9)	79 (58.1)	104 (60.9)	151 (60.9)	552 (60.6)	< 0.001 ***
Surgical (%)	41 (22.3)	35 (20.3)	31 (22.8)	49 (28.6)	36 (14.5)	206 (22.6)	< 0.001 ***
Trauma (%)	14 (7.6)	34 (19.8)	26 (19.1)	18 (10.5)	61 (24.6)	153 (16.8)	< 0.001 ***
Patients admitted from:							
The community (%)	82 (44.6)	71 (41.3)	70 (51.5)	68 (39.8)	100 (40.3)	391 (42.9)	< 0.001 ***
Another hospital (%)	32 (17.4)	17 (9.9)	18 (13.2)	19 (11.1)	44 (17.7)	130 (14.3)	< 0.001 ***
Other wards (%)	70 (38.0)	84 (48.8)	48 (35.3)	84 (49.1)	104 (42.0)	390 (42.8)	< 0.001 ***
Patients discharged home (%)	5 (2.7)	3 (1.7)	2 (1.5)	5 (2.9)	1 (0.4)	16 (1.8)	0.284
Patients transferred to other wards (%)	78 (42.4)	105 (61.0)	62 (45.6)	99 (57.9)	100 (40.3)	444 (48.7)	< 0.001 ***
Patients transferred to other hospital (%)	61 (33.2)	14 (8.1)	39 (28.7)	30 (17.5)	80 (32.3)	224 (24.6)	< 0.001 ***
Diabetes (%)	16 (8.7)	22 (12.8)	13 (9.6)	23 (13.5)	14 (5.7)	88 (9.6)	0.04923 **
Chronic renal failure (%)	9 (4.9)	12 (7.0)	6 (4.4)	9 (5.3)	9 (3.6)	45 (5.0)	0.636
Cirrhosis (%)	5 (2.7)	12 (7.0)	7 (5.2)	7 (4.1)	4 (1.6)	35 (3.9)	0.056 *
Sepsis/septic shock (%)	22 (12.0)	34 (19.8)	22 (16.2)	37 (21.7)	42 (17.0)	157 (17.3)	0.146
§ *** p<0.01; ** p<0.05; * p<0.1							

Table 2 Initial empiric antibiotic therapy receidev by patients surveyed

Antibiotics	N° pts. receiving antibiotic, N° (%) *	Proportion of total antibiotic use, % ç	Proportion of mono-therapy,% §	Proportion of combination therapy, % ^
Cephalosporins	**253** (33.4)	**20.7**	**40.1**	**12.3**
Cefazolin	85 (11.2)	7.0	17.8	2.3
Ceftriaxone	71 (9.4)	5.8	10.1	4.0
Cefotaxime	37 (4.9)	3.0	6.5	1.5
Ceftazidime	26 (3.4)	2.1	2.2	2.1
Cefepime	24 (3.1)	2.0	2.4	1.8
Cefotetan	8 (1.1)	0.7	1.1	0.4
Ceftizoxime	2 (0.3)	0.1	0.0	0.2
Piperacillin/tazobactam	**217** (28.6)	**17.7**	**20.5**	**16.8**
Glycopeptides	**147** (19.4)	**12.0**	**3.2**	**15.3**
Teicoplanin	107 (14.1)	8.7	2.4	11.7
Vancomycin	40 (5.3)	3.3	0.8	3.6
Fluoroquinolones	**133** (17.5)	**10.9**	**8.9**	**11.8**
Levofloxacin	79 (10.4)	6.5	4.3	7.5
Ciprofloxacin	53 (7.0)	4.3	4.6	4.3
Moxifloxacin	1 (0.1)	0.1	0.0	0.0
Carbapenems	**120** (15.8)	**9.8**	**6.2**	**11.6**
Meropenem	77 (10.2)	6.3	2.7	8.0
Imipenem	43 (5.7)	3.5	3.5	3.6
Penicillins	**102** (13.5)	**8.3**	**19.4**	**3.5**
Amoxicillin/clavulanate	52 (6.9)	4.3	10.5	1.5
Ampicillin/sulbactam	40 (5.3)	3.3	7.8	1.3
Oxacillin	5 (0.7)	0.4	0.5	0.4
Penicillin	2 (0.3)	0.2	0.3	0.1
Piperacillin	2 (0.3)	0.2	0.3	0.1
Ampicillin	1 (0.1)	0.1	0.0	0.1
Metronidazole	**99** (13.1)	**8.1**	**0.0**	**11.8**
Aminoglycosides	**53** (7.0)	**4.3**	**0.0**	**6.3**
Amikacin	21 (2.8)	1.7	0.0	2.5
Gentamicin	17 (2.2)	1.4	0.0	2.0
Netilmicin	8 (1.1)	0.7	0.0	1.0
Tobramicin	7 (0.9)	0.6	0.0	0.8
Clindamycin	**48** (6.3)	**3.9**	**0.8**	**5.4**
Others	**47** (6.2)	**3.8**	**1.0**	**5.2**
TOTALS		**100.0**	**100.0**	**100.0**

***** Many patients received more than one antibiotic, meaning that this column does not total 100%. Antibiotic classes received by > 5% of patients are shown; other antibiotics used in a few cases included macrolides, linezolid, chloramphenicol, and tigecycline.

ç Proportion of total 1223 antibiotic courses administered as initial empiric therapy

§ Proportion of monotherapy was calculated as the N° of patients receiving the antibiotic alone, as a proportion of all 369 patients receiving monotherapy

^ Proportion of combination therapy was calculated as the N° of patients receiving the individual antibiotic as a component of their combination therapy, as a proportion of the 388 patients receiving combination therapy

Table 3 Timing of initial clinical specimens*

TIME OF SAMPLING	**Hospital 1**	**Hospital 2**	**Hospital 3**	**Hospital 4**	**Hospital 5**	**Total** (%)
T0 (same day as clinical diagnosis)	**34**	**33**	**43**	**52**	**89**	**251** (27.6)
Cases with bacteraemia	2	4	2	12	22	42
Non-bacteraemic cases	32	29	41	40	67	209
Cases with a relevant-site specimen	31	32	36	43	70	212
T1 (within 10 days of clinical diagnosis)	**86**	**65**	**30**	**69**	**111**	**361** (39.6)
Cases with bacteraemia	9	8	0	10	42	69
Non-bacteraemic cases	77	57	30	59	69	292
Cases with a relevant-site specimen	67	50	28	53	68	266
Day > 10 (≥10 days after clinical diagnosis, or no sample	**64**	**74**	**63**	**50**	**48**	**299** (32.8)
Cases with bacteraemia	3	9	4	6	15	37
Non-bacteraemic cases	61	65	59	44	33	262
TOTAL	**184**	**172**	**136**	**171**	**248**	**911** (100.0)

* including patients not given any antimicrobial therapy

Table 4 Bacterial resistance (R) or susceptibility (S) to empirical therapy administered *

	Hospital 1		Hospital 2		Hospital 3		Hospital 4		Hospital 5		Total (%)	
CASES WITH ANY MICROBIOLOGICAL SAMPLE	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**
Empirically-treated patients with any T0 sample (n=235)	**8** (25.0)	**24** (75.0)	**14** (42.4)	**19** (57.6)	**11** (29.7)	**26** (70.3)	**19** (37.2)	**32** (62.8)	**36** (43.9)	**46** (56.1)	**88** (37.4)	**147** (62.6)
Cases with bacteraemia (n=34)	0	1	2	2	1	1	4	8	7	8	14	20
Non-bacteraemic cases (n=201)	8	23	12	17	10	25	15	24	29	38	74	127
Total treatments	**32**		**33**		**37**		**51**		**82**		**235**	
Total isolates from T0 samples	**35**		**40**		**54**		**63**		**121**		**313**	
Empirically-treated patients with any day T1-10 sample (n=347)	**46** (55.4)	**37** (44.6)	**40** (61.5)	**25** (38.5)	**15** (53.6)	**13** (46.4)	**30** (49.1)	**31** (50.9)	**61** (55.5)	**49** (44.5)	**192** (55.3)	**155** (44.7)
Cases with bacteraemia (n=54)	6	3	5	3	0	0	6	4	18	9	35	19
Non-bacteraemic cases (n=293)	40	34	35	22	15	13	24	27	43	40	157	136
Total treatments	**83**		**65**		**28**		**61**		**110**		**347**	
Total isolates from T1-10 samples	**112**		**86**		**45**		**85**		**221**		**549**	
CASES WITH A RELEVANT-SITE ^ CLINICAL SPECIMEN	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**	**R**	**S**
Empirically-treated patients with a relevant-site T0 sample (n=212)	**7** (22.6)	**24** (77.4)	**13** (40.6)	**19** (59.4)	**10** (27.8)	**26** (72.2)	**16** (37.2)	**27** (62.8)	**28** (40.0)	**42** (60.0)	**74** (34.9)	**138** (65.1)
Cases with bacteraemia (n=24) §	0	1	1	2	1	1	2	6	2	8	6	18
Non-bacteraemic cases (n=188)	7	23	12	17	9	25	14	21	26	34	68	120
Total treatments	**31**		**32**		**36**		**43**		**70**		**212**	
Empirically-treated patients with a relevant-site T1-10 sample (n=266)	**35** (52.2)	**32** (47.8)	**35** (70.0)	**15** (30.0)	**15** (53.6)	**13** (46.4)	**23** (43.4)	**30** (56.6)	**34** (50.0)	**34** (50.0)	**142** (53.4)	**124** (46.6)
Cases with bacteraemia (n=25)	2	2	5	1	0	0	2	4	4	5	13	12
Non-bacteraemic cases (n=241)	33	30	30	14	15	13	21	26	30	29	129	112
Total treatments	**67**		**50**		**28**		**53**		**68**		**266**	
Total patients	**184**		**172**		**136**		**171**		**248**		**911**	

* Defined as in Methods, p.5-6

^ i.e., taken from a body site corresponding to an infection recorded in the clinical records

§ Excluding coagulase-negative staphylococci which, based upon the clinical records, were not considered to be clinically significant

Table 5 Patient primary outcome* in relation to treatment adequacy among patients with a baseline relevant specimen

	TOTAL TREATED (WITH RELEVANT SPECIMEN)	TOTAL ADEQUATE (% of total treated)	DEATH (% of adequately treated)	SURVIVAL (% of adequately treated)	TOTAL INADEQUATE (% of total treated)	DEATH (% of inadequately treated)	SURVIVAL (% of inadequately treated)
Hospital 1	31	24 (77.4)	5 (20.8)	19 (79.2)	7 (22.6)	5 (71.4)	2 (28.6)
Hospital 2	32	19 (59.4)	4 (21.0)	15 (79.0)	13 (40.6)	8 (61.5)	5 (38.5)
Hospital 3	36	26 (72.2)	5 (19.2)	21 (80.8)	10 (27.8)	2 (20.0)	8 (80.0)
Hospital 4	43	27 (62.8)	3 (11.1)	24 (88.9)	16 (37.2)	6 (37.5)	10 (62.5)
Hospital 5	70	42 (60.0)	9 (21.4)	33 (78.6)	28 (40.0)	15 (53.6)	13 (46.4)
TOTAL	**212 (100.0)**	**138 (65.1)**	**26 (18.8)**	**112 (81.2)**	**74 (34.9)**	**36 (48.6)**	**38 (51.4)**

***** Defined as in Methods, p. 5-6

Figure captions

Figure. 1 Sites of clinically-diagnosed infections (grey) compared to number of specimens sampled (black), by site. Numbers indicate hospitals.

Figure 2 Duration of ICU stay in relation to adequacy of empirical treatment

Fig 1.pdf

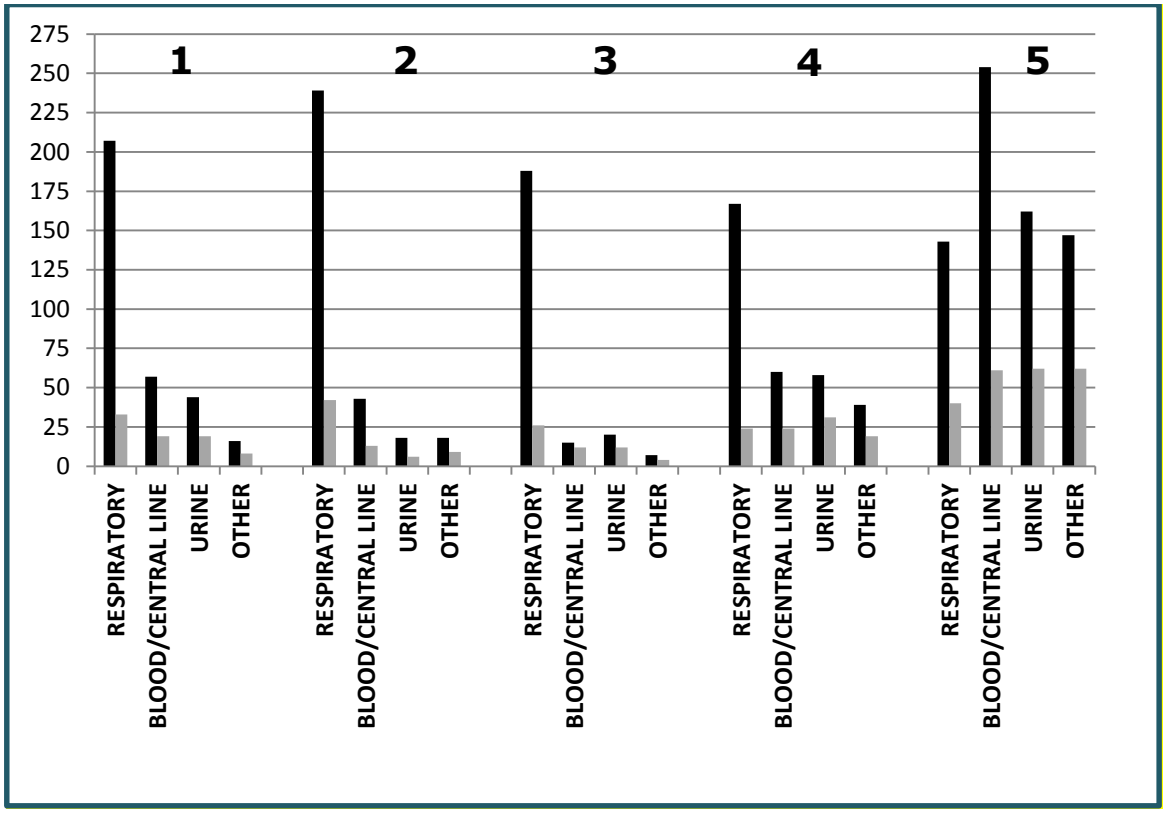
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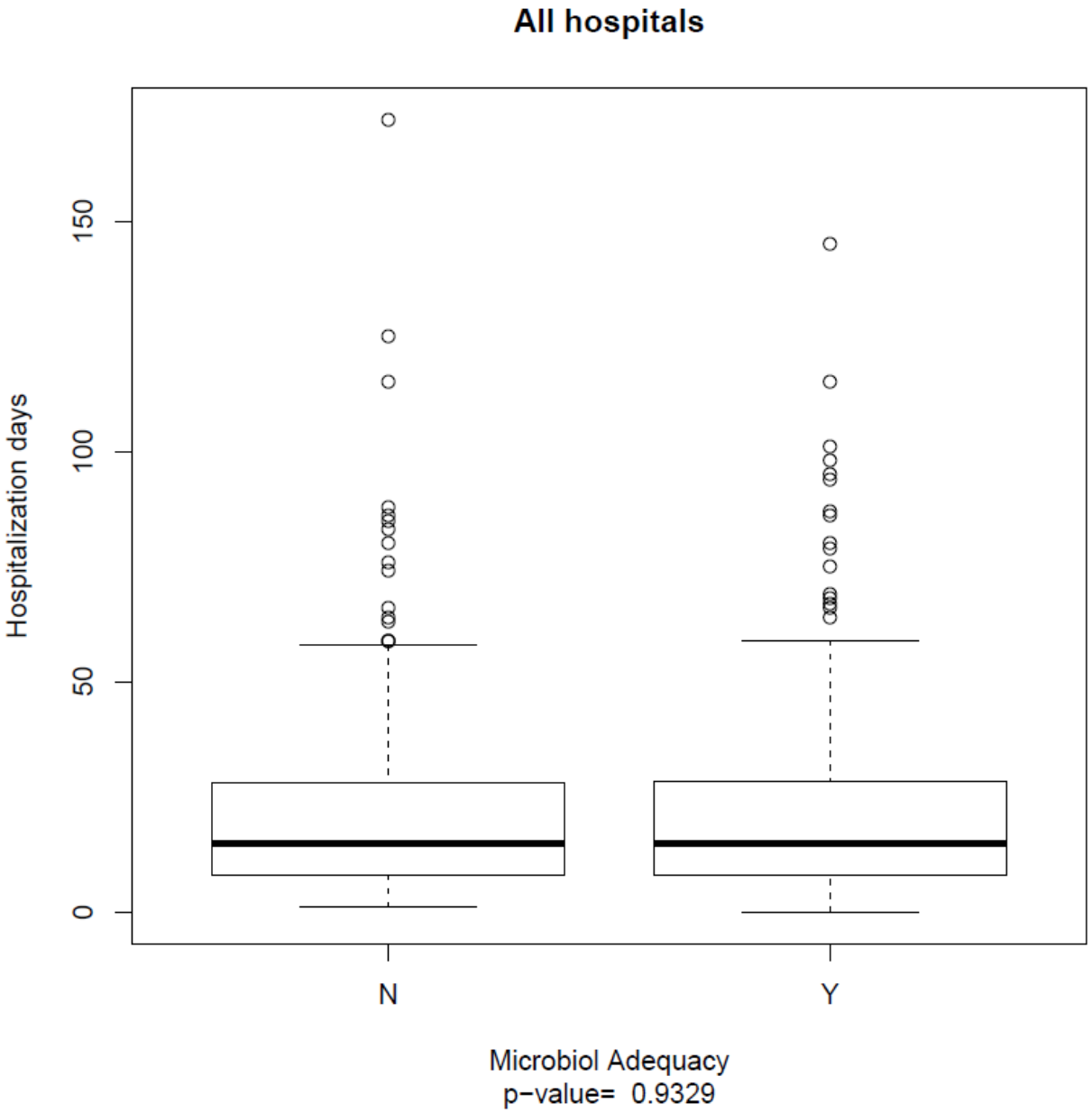
Fig 2.pdf


All hospitals
Hospitalization days
0
50
100
150
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Y
Microbiol Adequacy
p−value= 0.9329