Microbiological surveillance and antimicrobial stewardship minimise the need for ultrabroad-spectrum combination therapy for treatment of nosocomial infections in a trauma intensive care unit: An audit of an evidence-based empiric antimicrobial policy

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Background. Nosocomial infections are a major cause of morbidity in the critically injured, and the incidence of resistant strains of bacteria is increasing. Management requires a strategy that achieves accurate empiric cover without antibiotic overuse – a goal that may be achieved by surveillance and antibiotic stewardship.

Objectives. With the aim of minimising the use of empirical ultrabroad-spectrum combination antimicrobial prescriptions and reducing bacterial resistance, the level I Trauma Intensive Care Unit (TICU) at Inkosi Albert Luthuli Central Hospital (IALCH) in Durban employs stewardship and an antimicrobial policy based on surveillance. This study was undertaken with three aims: (*i*) to describe the spectrum and sensitivities of nosocomial pathogens in a level I TICU; (*ii*) to ascertain, based on surveillance data, how frequently initial empiric choice of antimicrobials was correct; and (*iii*) to determine how frequently ultrabroad-spectrum antimicrobials were prescribed and were actually necessary.

Methods. Over a 12-month period, all critically injured patients who underwent mechanical ventilation in the TICU were identified from a prospectively gathered database. Information regarding every specimen submitted to the National Health Laboratory Services (NHLS) situated at IALCH was extracted from the laboratory computer database. For each patient, bacterial isolates and antimicrobial susceptibility were identified using standard laboratory techniques. Empiric prescriptions for presumed nosocomial sepsis were identified from the hospital's computerised patient record system and compared with culture results. Acinetobacter species were regarded as colonisers and treatment not offered unless this was the sole isolate in the presence of signs of severe sepsis.

Results. Of 227 patients, 106 (46.6%) had 136 culture-positive isolates with a total of 323 pathogens (201 Gram-negative, 119 Gram-positive, 3 *Candida albicans*). There were 19 species of Gram-negative pathogens, of which 56% comprised Enterobacteriaceae. Extended spectrum beta-lactamase (ESBL) production was found in 6/31 (19%) *Escherichia coli coli* and 6/24 (25%) *Klebsiella* isolates. Staphyloccocal species accounted for 60% of the Gram-positive isolates, of which 18 were methicillin-resistant *Staphylococcus aureus* (MRSA). All *Candida* isolates were sensitive to fluconazole. One hundred and one empiric and 14 directed prescriptions were issued. Despite positive cultures, antimicrobials were not prescribed for 21 patients who had no evidence of sepsis. Excluding multidrug-resistant *Acinetobacter* isolates, there were 87 (93.5%) appropriate and 6 (6.5%) incorrect prescriptions. Ultrabroad-spectrum combination therapy (U-bSCT) was employed for 11 patients but was necessary in only 2.

Conclusions. When combined with regular bacterial surveillance, antimicrobial stewardship allows accurate empiric antimicrobial prescription with minimal need for ultrabroad-spectrum combination therapy. This policy can potentially reduce the emergence of multidrug-resistant pathogens, precluding the need for broad-spectrum antimicrobials and the attendant problems of overuse.

Multidrug-resistant organisms are an emerging threat in South Africa (SA).[1] Inappropriate prescriptions of broad-spectrum antimicrobials, multiple drug combinations, prolonged treatment and the lack of de-escalation are the main reasons, and Mendelson *et al.* warn that we are on course towards an era of untreatable bacterial infections.[2] Indiscriminate prescribing is common in SA intensive care units (ICUs),[3] driven by the fear that selecting the wrong antimicrobial to treat nosocomial infections will result in treatment failure and an increased mortality rate.[4,5] Ultrabroad-spectrum combination therapy (U-bSCT), whereby the initial empiric choice covers all possible pathogens, has been used injudiciously, with as many as 10 anti-infectives having been prescribed simultaneously. This policy is hazardous and promotes the development of multidrug-resistant (MDR) pathogens.[6]

Strategies to minimise the development of resistance (such as class restriction,[7] antibiotic cycling ('crop rotation')[8] and antimicrobial stewardship[9]) have been proposed. Unfortunately,

class restriction of specific agents and antibiotic cycling has had little effect and, with time, have demonstrated an increase in resistance to alternative drugs.[8-10] The most effective strategies are strict infection control measures and optimising both prophylactic and therapeutic antimicrobial use by surveillance, establishing a protocol, education and stewardship.[2,11] An effective empiric protocol based on knowledge of local microbiological patterns is essential, as is defining those risk factors that need ultrabroad-spectrum combination cover.

Our trauma intensive care unit (TICU) subscribes to stewardship and employs an empiric antimicrobial policy based on surveillance. The purpose of this study was threefold: (*i*) to describe the spectrum of nosocomial pathogens in a level 1 TICU; (*ii*) to ascertain, on the basis of monthly surveillance, how frequently the initial empirical choice of antimicrobials was correct; and (*iii*) to determine whether U-bSCT was warranted and, when used, how frequently it was actually necessary.

Patients and methods

This study was approved by the Bioethics Committee of the University of KwaZulu-Natal (BE 132/010) and was performed from 1 January to 31 December 2009 in the TICU at the Inkosi Albert Luthuli Central Hospital (IALCH) a tertiary/quaternary public service institution in Durban. The TICU contains 10 beds used exclusively for critically injured patients, providing support for both adults and children regardless of age. The study included all patients who underwent mechanical ventilation. The staff comprise 3 fulltime specialists trained in trauma surgery and critical care who decide admissions and make all treatment decisions.

All patients admitted to the TICU who underwent mechanical ventilation during the study period were entered into a computerised database. Information regarding every specimen submitted from patients in the database to the National Health Laboratory Services (NHLS) situated at IALCH was extracted from the laboratory computer database. Processing of specimens, identification of pathogens and antimicrobial susceptibility testing was carried out as per standard NHLS operating procedures.[12] All laboratory results were correlated with the patients' clinical condition and with adjunct investigations such as radiology, white cell counts and quantified procalcitonin levels, which were obtained from the hospital's Medicom information system. From the computerised prescription database, details of all patients who received antimicrobials were extracted and the selected empiric therapy analysed against bacterial sensitivity.

Ventilator-associated pneumonia (VAP) was defined as pneumonia occurring in a patient within 48 hours or more after intubation with an endotracheal or tracheostomy tube and which was not present before admission. The diagnosis was supported by presence of new pyrexia >38.4°C, changes on chest auscultation, new infiltrates on chest radiology, purulent endotracheal aspirate (ETA), a rise in white cell count, and elevated procalcitonin. Early-onset VAP was defined as occurring within 72 hours, and late-onset VAP beyond 72 hours following tracheal intubation. If multiple organisms were demonstrable in tracheal aspirates and VAP was suspected clinically, the choice of antimicrobial was made on the basis of the pathogen deemed to be most probably responsible. In this setting, *Acinetobacter baumannii* and other related species were regarded as colonisers; the organisms were usually multidrug-resistant and therapy was not selected on the basis of their sensitivities.

Vascular catheter-related bloodstream infection was defined by the clinical features of sepsis, growth of the same organism from peripheral blood and blood culture aspirated from either the intravenous (IV) catheter or a catheter segment, the absence of any other possible source of the infection, and resolution of the signs of sepsis within 24 hours of IV removal in the absence of antimicrobial or antipyretic therapy. A semiquantitative culture method for identifying IV catheter infection was employed to diagnose sepsis. Such bloodstream infection was managed by line removal alone unless the skin entrance site appeared septic. Replacement catheters were always inserted at a new site.

Urinary tract infection was defined by association of 2 of the following criteria: clinical signs of sepsis, pyuria ≥ 10 white blood cells (WBCs)/mm^3, urine culture of 10^5 colony-forming unit (CFUs)/ml, abnormal microscopy of urine, and the presence of nitrites on dipstick testing. The diagnosis of surgical site infection (SSI) was based on clinical examination, operative findings and microbiological analysis of specimens.

The antimicrobial protocol, established in conjunction with the Department of Medical Microbiology, for surgical prophylaxis and treatment of community- and hospital-acquired infections employed by the TICU is shown in Table 1. U-bSCT was not used as a matter of routine, and was instituted only if patients failed to respond within 48 hours to the first-line choice for suspected nosocomial infection, or if a recurrent episode of nosocomial sepsis was complicated by a sudden deterioration in organ function.

Results

During the study period, 227 patients were managed in the TICU: 144 with motor vehicle-related trauma (pedestrians 67, passengers 47, drivers 30), 36 for gunshot wounds, 26 non-vehicular blunt injury, and 21 stab wounds. There were 174 (76.7%) males and 53 (23.3%)

Table 1. Empirical policy for antimicrobial prophylaxis and therapy based on surveillance and co-existent organ dysfunction

	Prophylaxis	Therapy
Community-acquired		
Pneumonia		Amoxycillin/clavulanic acid
Peritonitis	Cefoxitin	Amoxycillin/clavulanic acid + gentamicin
Compound fracture	Cefazolin	Cloxacillin or moxycillin/clavulanic acid*
Hospital-acquired		
Pneumonia		Piperacillin/tazobactam + amikacin
		Piperacillin/tazobactam + ciprofloxacin†
Tertiary peritonitis		Piperacillin/tazobactam + amikacin
		Piperacillin/tazobactam + ciprofloxacin†
		(Fluconazole is added for foregut injury)
Catheter-related insertion site infection		Cloxacillin
Ultrabroad therapy		Meropenem + vancomycin + fluconazole‡

*If severe contamination.
†If acute kidney injury present.
‡If risk factors for fungal sepsis are present, which include penetrating foregut injury, repeated laparotomies, and prior treatment for nosocomial bacterial infections on more than 2 occasions.

females, with a mean age of 29.2 years (range 2 - 76). The median injury severity score (ISS) was 25 (IQR 16 - 29).

Of the 227 admissions, 106 (46.7%) yielded a total of 323 positive cultures of which 201 (62%) were Gram-negative, 119 (37%) Gram-positive, and 3 (1%) cultured *Candida albicans*. There were 19 different species of Gram-negative (Fig. 1) and 10 of Gram-positive (Fig. 2) organisms. Of the *Escherichia coli* isolates, 6 (19%) were
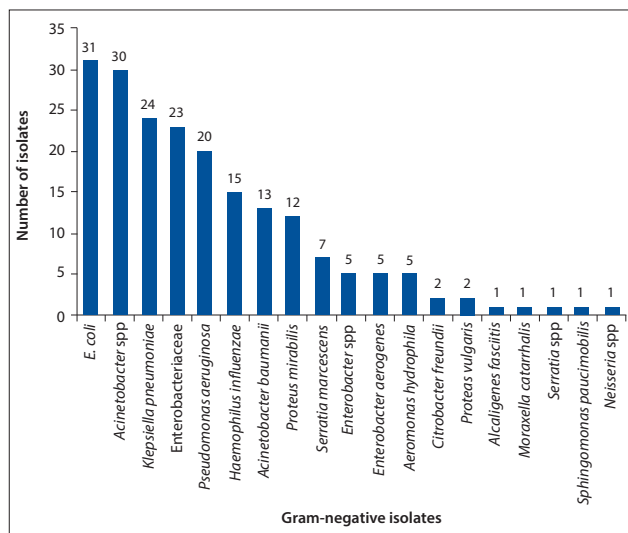

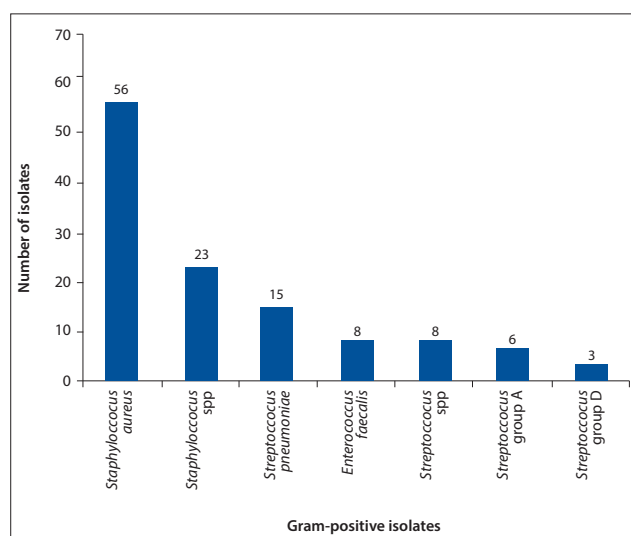*Fig. 1. Frequency and species of 201 Gram-negative isolates.*

Fig. 2. Frequency and species of most common Gram-positive isolates.

extended spectrum ß-lactamase (ESBL) positive, 19 (62%) were ESBL negative, and 6 (19%) were not tested. Routine testing of ESBLs was not performed if the organism was sensitive to amoxicillin/clavulanic acid. There were also 6 (25%) ESBL positive isolates of *Klebsiella pneumoniae*, 12 (50%) were ESBL negative, and 6 (25%) were not tested for the reasons outlined above. The 18 staphylococcal isolates that were reported as methicillin resistant arose from only 7 patients, 4 of whom had been transferred from other institutions.

Table 2 illustrates the distribution of positive cultures by specimen site, the Gram type of organism and number of patients. Table 3 shows the most common specific organisms isolated. Antimicrobial susceptibility testing was carried out on the various isolates to establish the accuracy of empiric treatment. All isolates were tested for their unique antimicrobial susceptibility patterns, which are illustrated in Tables 4 and 5 for the most common pathogens.

There were 101 empirical antimicrobial prescriptions prior to receipt of culture results, of which 90 (89%) involved first-line therapy consisting of piperacillin/tazobactam with either amikacin or ciprofloxacin, and 11 (11%) U-bSCT prescriptions using meropenem and vancomycin with the addition of fluconazole in 4. Fourteen directed prescriptions were issued according to culture results. In 21 instances, antimicrobials were not prescribed, despite positive cultures, owing to absence of clinical signs of sepsis (Fig. 3).

Of the 101 empiric prescriptions, 87 (86%) were correct, based on organism susceptibility, while 14 (14%) did not cover the isolated pathogens. Of the latter, there were 8 isolates of MDR *Acinetobacter* (7 endotracheal aspirates, 1 blood culture), of which 3 were treated with empiric U-bSCT and 5 received empiric first-line therapy. The former group of subjects all died, whilst the latter survived. Excluding these 8 *Acinetobacter* isolates as per unit policy there were therefore 87/93 (94%) correct and 6/93 (6%) incorrect empiric prescriptions (Fig 3). The latter consisted of inadequate cover for *Candida* species (2), ESBL-producing *E. coli* (2), ESBL-producing *Klebsiella* (1) and *Serratia* (1). Of the 11 empiric ultrabroad-spectrum therapy prescriptions, 6 isolates were piperacillin/tazobactam-sensitive, in 3 multidrug-resistant *Acinetobacter* was the primary pathogen isolated, while the remaining 2 consisted of ESBL-producing *E. coli* and ESBL-producing *Klebsiella* sensitive to ciprofloxacin and meropenem respectively. Therefore only 2 of the 11 prescriptions were appropriate. There were 25 positive culture isolates in the 21 patients who did not receive antimicrobials; tracheal aspirates accounted for 62%, central venous catheter tips and surgical site specimens for 14% each, and blood cultures for 10%. There were no deaths in this group of 25, despite the absence of therapy.

Among the 227 admissions, there were 40 (18%) deaths, of whom 16 (40%) subjects had undergone antimicrobial treatment

Table 2. Distribution of positive cultures by specimen site

Specimen	Gram-negative *n* (%)	Gram-positive *n* (%)	*C. albicans n* (%)	Total *n* (%)	Number of patients*
ETA	88 (65)	47 (34)	1(1)	136 (42.1)	71
SSI	68 (67)	32 (32)	1(1)	101 (31.3)	44
CVC	17 (39)	26 (59)	1(2)	44 (13.6)	36
Blood	21 (66)	11 (34)		32 (9.9)	24
Urine	7 (70)	3 (30)		10 (3.1)	10
Total	201 (62)	119 (37)	3(1)	323 (100)	

ETA = endotracheal aspirate; SSI = surgical site infection; CVC = central venous catheter.
*Some patients had more than one site of sepsis.

Table 3. The most common isolates (≥15) per specimen site

Pathogen (n)	Lower respiratory tract infection n (%)	Surgical site infection n (%)	Bloodstream infection* n (%)
Gram-negative			
E. coli (31)	8 (25.8)	17 (54.8)	4 (12)
K. pneumoniae (24)	13 (54.1)	6 (25)	5 (20.8)
Acinetobacter spp. (30)	17 (56.6)	6 (19.3)	7 (23.3)
E. cloacae (23)	6 (26)	6 (26)	8 (34.7)
P. aeruginosa (20)	7 (35)	13 (65)	0 (0)
A. baumannii (13)	6 (46)	3 (23)	4 (30.7)
H. influenzae (15)	13 (86.6)	1 (6.6)	1 (6.6)
Gram-positive			
S. aureus (56)	33 (58.9)	12 (21.4)	11 (19.6)
S. spp. (23)	1 (4.4)	0 (0)	22 (95.6)
S. pneumoniae (15)	10 (66)	1 (6.6)	4 (26.6)

*Bloodstream infection includes both blood cultures and catheter-related infections.

Table 4. Antimicrobial susceptibility of the more common (≥15 isolates) Gram-negative organisms

Organism (number of isolates)	Antimicrobial sensitivity n (%)					
	Mer	Pip/taz	Amik	Cipro	Genta	Amoxy-clav
E. coli (31)	30 (97)[†]	28 (90)	28 (90)	26 (84)	29 (94)	14 (45)
Acinetobacter spp. (30)	3 (10)	4 (13)	13 (43)	3 (10)	4 (13)	0 (0)
K. pneumoniae (24)	22 (92)*	19 (79)	20 (83)	18 (75)	16 (66)	14 (58)
E. cloacae (23)	22 (96)[†]	21 (91)	21 (91)	19 (83)	18 (78)	0 (0)
P. aeruginosa (20)	19 (95)[†]	11 (55)-S 9 (45)-I	19 (95)	15 (75)	14 (70)	0 (0)
H. influenzae (15)				14 (93)[†]		15 (100)
A. baumanii (13)	3 (23)	2 (15)	9 (69)	6 (46)	2 (15)	0 (0)
P. mirabilis (12)	12 (100)	10 (83)	12 (100)	10 (83)	11 (92)	10 (83)

Mer = meropenem; Pip/taz = piperacillin/tazobactam; Amik = amikacin; Cipro = ciprofloxacin; Genta = gentamicin; Amoxy-clav = amoxycillin/clavulanic acid; S = sensitive; I = intermediate sensitivity.
*Two not tested.
[†]One not tested.

Table 5. Antimicrobial susceptibility of the more common (≥15 isolates) Gram-positive organisms

Organism (number of isolates)	Antimicrobial sensitivity n (%)						
	Amp	Clinda	Clox	Eryth	Genta	Pen	Vanco
S. aureus (56)	9 (16)	40 (71)	38 (68)	40 (71)	35 (62)	6 (11)	56 (100)
Staphylococcus spp. (23)	5 (22)	13 (56)	8 (35)	9 (39)	7 (30)	3 (13)	22 (96)*
S. pneumoniae (15)	10 (67)	2 (13)	0 (0)	8 (53)	0 (0)	14 (93)	2 (13)[†]

Amp = ampicillin; Clinda = clindamycin; Clox = cloxacillin; Eryth = erythromycin; Genta = gentamicin; Pen = penicillin; Vanco = vancomycin.
*One not tested.
[†]Twelve not tested.

for presumed nosocomial sepsis. Seven (44%) of the 16 deaths were in the incorrect treatment group, the isolates revealing MDR *Acinetobacter* in 3, *Candida* in 3 and ESBL-producing *E. coli* in 1. In these individual patients, *C. albicans*, susceptible to fluconazole, was isolated on day 3 from a tracheal aspirate, on day 5 from a central venous catheter tip, and on day 7 from abdominal fluid; and *E. coli* on day 3 from a tracheal aspirate and blood culture. All patients in whom

Candida was isolated had abdominal gunshot wounds with hollow visceral injuries; in 1, *Candida* was cultured from abdominal fluid at relaparotomy despite administration of prophylactic fluconazole for 48 hours. The patient in whom *E. coli* was cultured had sustained severe traumatic brain and chest injuries and multiple compound fractures (managed by decompressive craniectomy and damage control orthopaedic surgery).
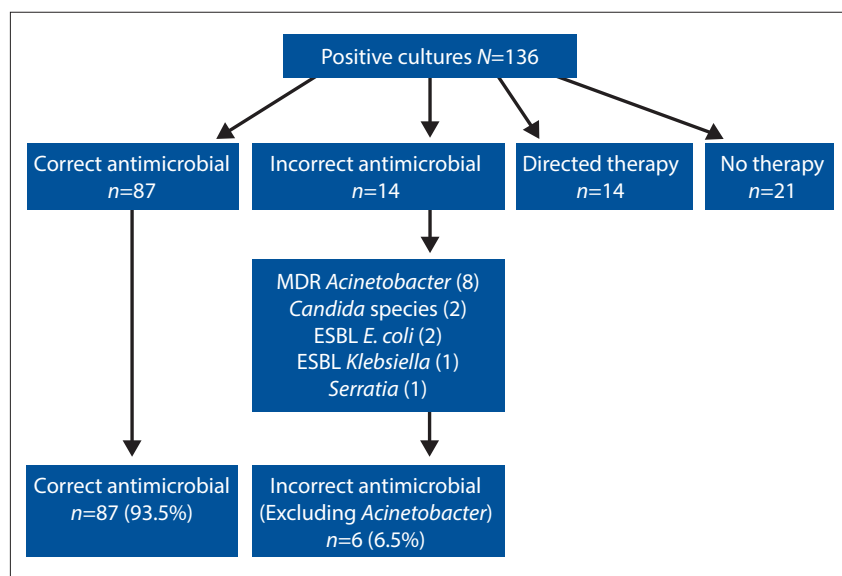
Fig. 3. Correct, incorrect and directed prescriptions for nosocomial sepsis.

There were 24 (20%) deaths in 121 patients who did not suffer nosocomial sepsis, and 16 (15%) in the 106 in whom positive isolates were recovered. Of the former, 11 deaths occurred either during resuscitation or emergency surgery, these individuals having not reached ICU. Excluding these early deaths, there was no significant difference in mortality between those with or without nosocomial sepsis ($p=0.55$).

Discussion

In this study, Gram-negative organisms of the *Enterobacteriaceae* family predominated, closely followed by *Pseudomonas*. Gram-positive species from which *Staphylococcus aureus* was isolated most frequently were less common. Although the flora may be shown to be similar, the extent and specific detail of bacterial resistance to antimicrobials varies considerably in reported series. While intrinsic genetic coding accounts for some instances of resistance, the most common cause is the overuse of broad-spectrum agents and selective pressure on the micro-organism. The pathogens causing most concern are more easily remembered by the mnemonic ESKAPE, i.e. *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *Acinetobacter* spp., *Pseudomonas aeruginosa*, and *Enterobacter* spp.[13] The most common mechanism of resistance is the production of ESBLs by Enterobacteriaceae, especially *K. pneumoniae* and *E. coli*. This may arise in almost 50% of *Klebsiella* isolates,[14] and their prevalence therefore dictates empiric antimicrobial choice. The low prevalence of MRSA in our cohort reflects the lack of

exposure to antimicrobials in the general population; we have yet to encounter vancomycin resistance, hence the use of this glycopeptide as first-line therapy. Not one patient died from this infection despite the fact that no therapy was offered to 4 of the 7 patients. It has recently been suggested that this pathogen may not confer direct attributable mortality.[15]

Fungal infections are of increasing importance in ICUs,[16] and in this study possibly accounted for 3 deaths among those offered inappropriate therapy. *Candida* is a normal commensal of the stomach and proximal intestine and, although we cannot present hard evidence, our experience of treating penetrating abdominal trauma with foregut injuries caused by gunshot wounds, indicates that prophylaxis for *Candida* is warranted, especially in those requiring ICU management. Establishing the diagnosis of invasive candidiasis may be difficult, and the burden of HIV infection in SA, with the potential for *Candida* overgrowth, adds further credence to this premise. Failure to provide fungal cover constitutes an act of omission in our view.

It is the policy of the TICU not to treat MDR *A. baumannii* or related species if occurring in a mixture of flora. There are several evidenced-based reasons for this policy: firstly, *Acinetobacter* is a long-term coloniser and can persist on a variety of inanimate surfaces for prolonged periods of time; secondly, *Acinetobacter* species have historically been considered organisms of low virulence and pathogenicity, and attributable morbidity and mortality has been an ongoing debate for the past 30 years, chiefly because of

the difficulty of differentiating colonisation from infection.[17] Recent work, however, suggests that mutant strains possess specific capsular proteins that confer increased virulence and resistance to the effects of complement in human serum and ascitic fluid;[18] and thirdly, most *Acinetobacter* species are inherently resistant to all but a few antimicrobials, and embarking on therapy would necessitate the use of U-bSCT and the risk of treating colonisation rather than true infection, which in turn would lead to emergence of other MDR organisms. In addition, *Acinetobacter* has the ability to develop resistance even during directed therapy,[17] and the isolation of subpopulations that are resistant to colistin is of serious concern. Although ethically debatable, this practice conforms to the principle of social justice over autonomy and complements the view of Mendelson *et al.*[1] that inappropriate and unnecessary prescriptions of broad-spectrum antimicrobials may ultimately result in an era of untreatable bacterial infections.

Excluding *Acinetobacter* from the empiric equation, our choice of antimicrobials was correct in more than 90% of instances, indicating that frequent surveillance and stewardship promote a more rational and restricted policy of antimicrobial use and an infrequent resort to U-bSCT. It should be noted that protagonists of such therapy (that provides antimicrobials effective against ESBL-producing Gram-negatives, MRSA and *Candida*) cite improved outcomes and claim that resistance will not increase, provided that it is used for brief periods, and the spectrum narrowed once there is microbiological confirmation. We would suggest otherwise. Firstly, most patients would respond to such broad therapy and their clinicians continue with a full course of treatment with inevitable pressure on the microbial environment. Secondly, culture results may not be available within 48 hours, again resulting in protracted, but unnecessary, broad-spectrum therapy. Thirdly, given the natural history of the selection of resistant strains of bacteria, why should the response to frequent use of broad-spectrum antimicrobials be any different in the future? Although the length of treatment might be abbreviated by de-escalation, total antimicrobial use will inevitably increase with detrimental consequences.[1]

In our cohort, only 11 prescriptions required U-bSCT, of which 9 were not warranted. Excluding *Acinetobacter*, regarding the deaths in patients not offered U-bSCT, there were 2 *Candida* isolates and

one ESBL-producing *E. coli*. Of the former, as mentioned above, failure to immediately prescribe antifungal therapy accounted for the one potential attributable death. Given such data, we suggest that, with an active surveillance programme and empiric antimicrobial policy, blanket cover is rarely indicated. Kollef makes the additional salient statement that the empiric choice of antimicrobials should cover the most likely pathogens endemic to the specific location.[19] It is important to note that the statement does not say **all** pathogens, and prescriptions cannot be based on uncommon organisms unless the situation dictates the need. To this end, antimicrobial stewardship is of paramount importance, especially in areas with frequent antimicrobial use. There are many challenges to successful stewardship, but the aims are education, prevention of antimicrobial overuse, and minimising the development of resistance.[20] Pivotal to success are interested clinicians and microbiologists, knowledge of local resistance patterns, and an antimicrobial policy that optimises the choice, dose and duration of therapy.

Seventy years ago, Sir Alexander Fleming[21] correctly predicted the development of antimicrobials when he stated, 'The intensive research which penicillin has stimulated may bring forth others as good, or even better, or the chemists may be able to modify the penicillin molecule so that its power is increased or its limitations are removed. There is still plenty of scope for further advance'. In the same book edited by Fleming, however, Porritt and Mitchell[22] made the pessimistic prophesy: 'As with sulphonamides, the prophylactic use of penicillin will carry the risk of breeding resistant strains, a matter of serious practical importance that cannot be dismissed lightly'. Unfortunately, the indiscriminate use of the drugs that Fleming predicted has promoted the emergence of resistance to even the most broad-spectrum antimicrobials. While Fleming's prediction that there is scope for further advance in the manufacture of new antimicrobials undoubtedly held true in the first half of the 20th century, the same cannot be said for now. There are few, if any, new avenues[1,2] and strict measures must be implemented to enforce infection control and curb indiscriminate and inappropriate antimicrobial prescribing.[2,3]

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