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Cross-border antibiotic resistance patterns in trauma patients

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ABSTRACT

Background: Antibiotic resistance is a growing problem worldwide, with differences in regional resistance patterns driven by variance in antibiotic stewardship. Hospitals along the United States-Mexico border increasingly identify resistance, raising concern for transfer of drug-resistant organisms across the border.

Methods: This retrospective review evaluated trauma admissions between March 2011 and August 2015. Patients were included if cultures were obtained during the first 3 days of hospitalization to limit analysis of hospital-acquired bacteria. A matched Mexico and US cohort subanalysis was later compared to eliminate bias in time from injury to culture.

Results: Among 115 Mexico and 1,149 US patients, Mexico patients were younger (mean 44.3 vs 60.4 years), had a higher median injury severity score (21 vs 10), and longer hospital durations of stay (mean 11.6 vs 5.5 days). These differences resolved in the matched analysis. Infections were more common in Mexico than US patients in the matched cohort, and resistant infections including resistant gram-negative infections were more common in Mexico patients in both the matched and overall cohorts. The only resistant organism identified in matched US patients was methicillin-resistant *Staphylococcus aureus.* Extended-spectrum β-lactamase *Klebsiella* was found only in patients from Mexico. Additional risk factors for resistance in the matched cohorts included injury in Mexico, ≥2 days from injury to admission, and tracheostomy placement in Mexico.

Conclusion: Antibiotic resistance is more common in patients initially treated in Mexico healthcare facilities than those treated exclusively in the United States and may require alternative empiric treatment. Global initiatives to improve antibiotic stewardship will be critical to limit the continued rise in drug-resistant infections.

Introduction

Drug resistant (DR) organisms are increasingly common worldwide, with different regions demonstrating significant variance in commonly effected organisms and specific resistance patterns.[1–3] Regional variances are driven by both societal and healthcare factors, including levels of antibiotic stewardship (human and veterinary), infection control practices, environmental measures, and public education.[4–6] Of particular concern are resistant gram-negative organisms, which are increasingly prevalent in Latin America and account for a higher percentage of infections than in the United States or Canada.[7,8] Patients initially treated in higher-prevalence areas are known to be at risk of active DR infections, and screening protocols for transfer patients have been established in some centers.[2,9] Hospitals along the US-Mexico border have also demonstrated increasing resistance patterns, raising concern for international transfer of DR organisms.[10]

The San Ysidro Land Port of Entry in San Diego, CA, the busiest land port of entry in the Western Hemisphere, currently processes an average of 90,000 northbound travelers daily.[11] This port of entry is also a common site of cross-border transfer of patients seeking healthcare in the United States, including ≈400 trauma patients per year who initially receive care in Mexico prior to transfer into the San Diego County trauma system. During clinical care of these patients transferred from Mexico, we noted a high prevalence of DR organisms that were not sensitive to our standard empiric antibiotic treatment. To our knowledge, no studies specific

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to DR infections in US surgical or trauma patients initially treated abroad have been published. We hypothesized that patients transferred to a US trauma center after initial treatment in a healthcare facility in Mexico will have a higher prevalence of infections due to antibiotic-resistant organisms, including DR gram-negative bacteria.

Methods

Data source, study setting, and participants

The registry of our American College of Surgeons-verified level I trauma center was retrospectively reviewed for all patients admitted to the trauma service from March 1, 2011 to August 30, 2015. For the overall cohort, we collected all patients who had at least 1 culture (beyond a methicillin-resistant *Staphylococcus aureus* nasal swab) sent during the first 3 days of their hospitalization in the United States, to evaluate infections present on admission and limit analysis of organisms acquired in our facility. Patients were excluded only if the country in which they were initially treated could not be determined. We also performed a post-hoc matched cohort analysis where patients from Mexico and the US were matched 1:1 for demographic characteristics including, in order of priority, days from injury to culture, presence of tracheostomy at time of cultures, injury severity score (ISS), age, sex, ventilator days, intensive care unit duration of stay, and mechanism of injury. For this cohort, we evaluated cultures sent during the first 3 days of hospitalization in our facility for patients initially treated in Mexico, and during an equivalent 3-day window from time of injury for their matched US partner. This study was approved by the local Institutional Review Board with waiver of consent. All data collection and storage occurred in compliance with Health Insurance Portability and Accountability Act of 1996 rules and regulations.

Data collection

Data were collected from both the trauma registry and the electronic health record, including demographics, comorbid conditions, mechanism and location of injury, care provided prior to admission (when available), injuries, procedures, culture results for the timeframes defined above, and outcomes. All culture results were reviewed to remove duplicate results and classify results as true infections versus colonization. For the purposes of this study, only bacterial infections were reviewed while all fungal and yeast culture results were excluded. For urinary tract infections, cultures were designated as true infections only if >100,000 colonies/mL were present. For respiratory infections, cultures were characterized as ventilator-associated pneumonia (VAP), nonventilator associated pneumonia, or no infection. VAP was identified only if the 2016 National Trauma Data Standard VAP guidelines were met.[12] Nonventilator associated pneumonia was counted if diagnosed and treated by the trauma team at the time of care. Blood culture results were individually reviewed if positive for coagulase-negative *Staphylococcus* or if only 1 of multiple culture bottles yielded positive results. Final determination of true infection was determined by consensus of multiple authors.

Cultures were labeled with specific resistance patterns if such a pattern was identified on the final microbiology report based on standard laboratory procedures. This was the case for all instances of extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae*, Methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus faecium* (VRE). Resistance was inferred for other organisms if specific criteria were met as follows: 1) for multidrug-resistant (MDR) *Pseudomonas aeruginosa* (MDR *Pseudomonas*), resistance to ≥1 agent in ≥3 of the following classes by Clinical and Laboratory Standards Institute- or Phoenix-defined minimum inhibitory concentration 90 breakpoints: monobactams, antipseudomonal cephalosporins, β-lactam/β-lactamase inhibitor combinations, carbapenems, fluoroquinolones, aminoglycosides, or lipopeptides; 2) for MDR *Acinetobacter spp.* (MDR *Acinetobacter*), resistance to ≥1 agent in ≥3 of the following classes by Clinical and Laboratory Standards Institute- or Phoenix-defined minimum inhibitory concentration 90 breakpoints: β-lactam/β-lactamase inhibitor combinations, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, tetracyclines, antifolate, or lipopeptides.

Outcomes

The primary outcome was prevalence of antibiotic resistance in Mexico patients compared to those treated only in the United States, both in the overall cohort and in the matched cohort analysis. Secondary outcomes included specific resistance patterns, infection subtypes, and additional risk factors for resistant infection.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, version 24.0). In bivariate analysis, we used the Pearson χ^2 test for categorical variables. For independent variables that did not meet the assumptions for the χ^2 test (ie, <5 observations), the Fisher exact test was used to test the association. Continuous variables were compared using the independent samples Student's *t* test if they met normality assumptions, and with the Mann-Whitney *U* test if they did not. Variables were considered for inclusion in the logistic regression model if their bivariate *P* value was <.2. Model reduction was performed using backward stepwise regression with criteria for entry set at $P < .05$ and criteria to remove from the model at $P > .1$. Variables that did not meet *P* value criteria were kept in the model if they were deemed to be important confounders or if their exclusion caused a significant change in model performance.

Results

A total of 1,149 US and 115 Mexico patients met criteria and were included in the overall cohort analysis. Mexico patients were younger, more likely to be Hispanic, and had a longer delay between the time of injury and admission to our hospital, as expected (Table I). Mexico patients were found to have a significantly higher ISS as well as longer hospital and intensive care unit duration of stays and more ventilator days. There was no statistically significant difference in mortality. We were unable to obtain records regarding pre-transfer antibiotic use for the vast majority of Mexico patients, but could confirm antibiotic usage in 13.9% ($n = 16$). Of these, 7 received a single antibiotic, 4 received 2 antibiotics, and 5 received 3 antibiotics; at least 13 different antibiotics were used. There were 3 patients for which records demonstrated that antibiotics had been given, but the specific drug could not be identified. The most common antibiotics given included ceftriaxone, levofloxacin, amikacin, and meropenem.

Regarding culture results, for the overall cohort US patients had a total of 2,875 cultures sent compared to 406 in Mexico patients, with no statistically significant difference in the percentage of positive cultures or patients with positive cultures (Table II). Mexico patients were more likely to have respiratory infections (54.9% of all infections Mexico patients vs 20.7% US patients, $P < .001$), while urinary tract infections were more common in US

Table I
Demographics and outcomes, by country and cohort

	MEX (n = 115)	Overall US (n = 1,149)	*P* value	Matched US (n = 115)	*P* value
Age, y (mean [SD])	44.3 (19.5)	60.4 (22.3)	<.001	44.5 (19.8)*	.927
Male, *n* (%)	79 (68.7)	691 (60.1)	.073	84 (73.0)*	.468
Ethnicity, *n* (%)					
White	27 (23.5)	577 (50.2)		52 (45.2)	
Black	1 (0.9)	69 (6.0)	<.001	6 (5.2)	.010
Hispanic	77 (67.0)	371 (32.3)		44 (38.3)	
Blunt trauma, *n* (%)	103 (89.6)	1,079 (93.9)	.143	107 (93.0)*	.349
Days, injury to arrival	2 (3)	0 (0)	<.001	0 (0)	<.001
Days, injury to first culture	2 (3)	0 (0)	<.001	3 (3)*	.683
ISS	21 (15.5)	10 (15)	<.001	22 (15)*	.806
Mortality, *n* (%)	13 (11.3)	89 (7.7)	.248	15 (13)	.687
Hospital LOS, d	11.6 (20.0)	5.5 (9.0)	<.001	12.9 (17.9)	.976
ICU LOS, d	5 (12)	2 (5)	<.001	5 (11)*	.357
Ventilator days	2 (10)	0 (3)	.002	3 (10)*	.535

SD, standard deviation; *ICU*, intensive care unit; *MEX*, Mexico; *LOS*, length of stay.
Values are median (interquartile range) unless otherwise specified.
* Matched for this criterion.

Table II
Culture results and resistance patterns, by country and cohort

	MEX (n = 115)	Overall US (n = 1,149)	*P* value	Matched US (n = 115)	*P* value
Number of cultures sent	406	2,875	—	420	—
Positive cultures	51 (12.6)	357 (12.4)	.808	33 (7.9)	.035
Patients with ≥1 positive culture	40 (34.8)	319 (27.8)	.188	28 (24.3)	.120
Number of total organisms grown	67	411	—	37	—
Infection site, *n* (% of total positive cultures)					
Blood	6 (11.8)	63 (17.7)	.296	4 (12.1)	.961
Respiratory	28 (54.9)	74 (20.7)	<.001	12 (36.4)	.099
Urine	8 (15.7)	191 (53.5)	.001	11 (33.3)	.077
Body site	9 (17.7)	27 (7.6)	.076	5 (15.2)	.768
Cerebrospinal fluid	0 (0)	1 (0.3)	NS	1 (3.0)	NS
Line tip	0 (0)	1 (0.3)	NS	0 (0)	NS
Organism, *n* (% of total organisms grown)					
Escherichia coli	10 (14.9)	133 (32.4)	<.001	5 (13.5)	.846
Klebsiella sp.	9 (13.4)	30 (7.3)	.166	2 (5.4)	.158
Staphylococcus aureus	18 (26.9)	47 (11.4)	<.001	7 (18.9)	.369
Enterococcus sp.	1 (1.5)	6 (1.5)	.984	0 (0.0)	.321
Pseudomonas sp.	6 (9.0)	12 (2.9)	.099	4 (10.8)	.761
Acinetobacter sp.	1 (1.5)	2 (0.5)	.513	0 (0.0)	.321
Other	22 (32.8)	181 (44.0)	.086	19 (51.4)	.065
Overall distribution			<.001		.086
Resistance, *n* (% of each organism grown)					
Escherichia coli	3 (30)	17 (12.8)	.294	0 (0)	.081
Klebsiella sp.	5 (55.6)	0 (0)	.013	0 (0)	.013
Staphylococcus aureus	7 (38.9)	9 (19.1)	.101	3 (42.9)	.862
Enterococcus sp.	0 (0)	3 (50)	NS	—	—
Pseudomonas sp	2 (33.3)	0 (0)	.174	0 (0)	.175
Acinetobacter sp.	1 (100)	0 (0)	NS	—	—
Gram-negative resistance	11 (42.3)	17 (9.6)	.003	0 (0)	<.001
Total resistance, *n* (% all organisms grown)	18 (26.9)	29 (7.1)	<.001	3 (8.1)	.010

MEX, Mexico.
Gram-negative resistance: *E. coli, Klebsiella, Pseudomonas, Acinetobacter* species.
Values are a number (%) unless otherwise specified.

patients (53.5% US patients vs 15.7% Mexico patients, $P < .001$). When evaluating the specific organism responsible for infection, *E. coli* infections were more common in US patients (32.4% US patients vs 14.9% Mexico patients, $P < .001$), while *S. aureus* was more common in those from Mexico (26.9% Mexico patients vs 11.4% US patients, $P < .001$).

When resistance patterns were examined, *Klebsiella* organisms from Mexico patients were more likely to harbor ESBL properties than *Klebsiella* isolated from US patients in the overall cohort (55.6% of all Mexico patient's *Klebsiella* showed ESBL vs 0% in US patients, $P = .013$; Table II, Fig 1). Mexico patients also had a higher prevalence of resistance in gram-negative infections overall (*E. coli, Klebsiella sp., Pseudomonas sp.,* and *Acinetobacter sp.* grouped, 42.3% Mexico patients vs 9.6% US patients, $P = .003$). Resistant bacteria (ESBL *E. coli* and *Klebsiella*, MRSA, VRE, and MDR *Pseudomonas* and *Acinetobacter*) comprised 26.9% of all organisms grown in Mexico patients compared to only 7.1% of total organisms in US patients ($P < .001$). When gram-negative organisms were surveyed for sensitivity to common antibiotics, organisms from Mexico patients were significantly less likely to be sensitive to ceftriaxone,

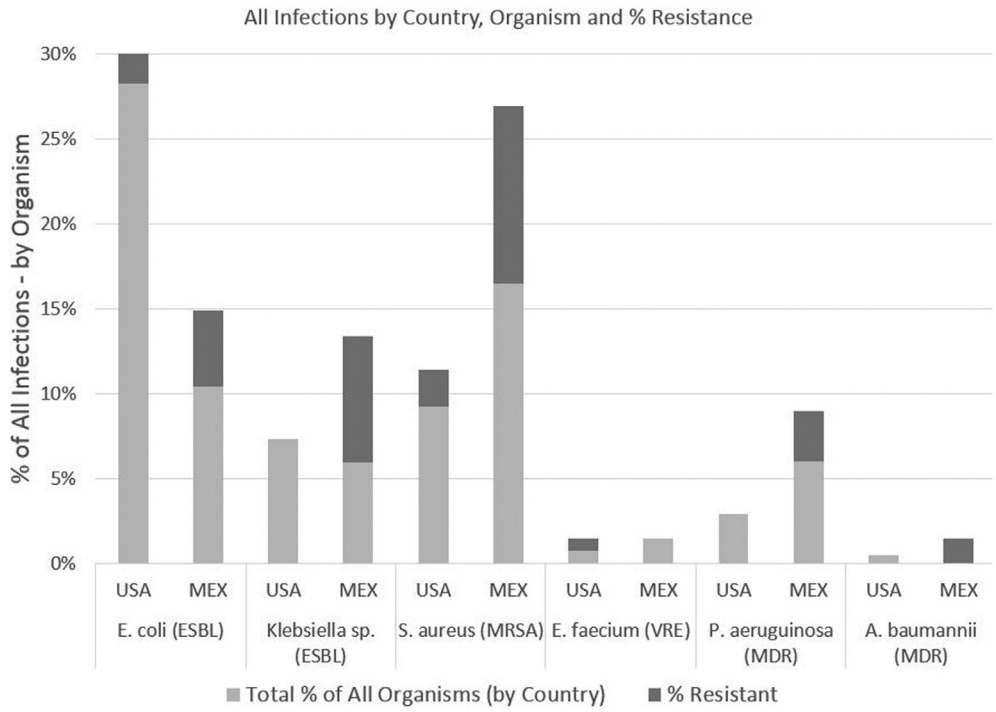

Fig 1. United States versus Mexico culture results by organism and the percentage of each organism that is resistant, for the overall cohort. Types of resistance indicated with each organism.

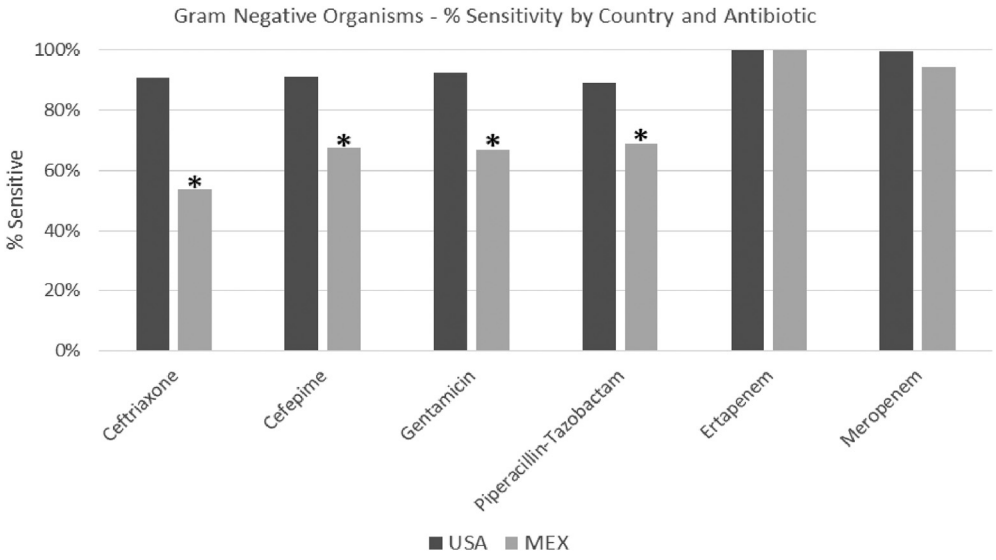

Fig 2. United States versus Mexico sensitivity of gram-negative organisms to common antibiotics in the entire cohort. *$P < .05$ vs US.

cefepime, gentamicin, and piperacillin-tazobactam than those from the United States (Fig 2). There were no significant differences in antibiotic sensitivities for ertapenem and meropenem.

We then examined the overall cohort of patients to identify risk factors for infection and resistant infection. Logistic regression identified injury in Mexico, female sex, pre-existing malignancy, and cirrhosis as risk factors for overall infection (Table III). Risk factors for resistant infection included injury in Mexico, pre-existing smoking, tracheostomy placed at the referring hospital, and ≥2 days from injury to admission (Table IV). The Mexico cohort was also analyzed separately, as some risk factors such as antibiotic administration prior to admission were rare in the US population. For the Mexico patients alone, bivariate regression identified Foley catheter, central line, and tracheostomy placement in Mexico and any antibiotics given in Mexico as risk factors for resistant infection (Table IV). Logistic regression indicated that tracheostomy placement in Mexico was the most significant predictor of developing an infection with a resistant organism (odds ratio [OR] 18.68, $P = .01$).

A matched cohort, consisting of the same 115 Mexico patients matched 1:1 to 115 US patients as described in the Methods was then analyzed. The demographics of the matched cohort demonstrated that patients were well matched, with the only statistically significant differences being ethnicity and days from injury to arrival (Table I). While the number of cultures sent was similar

Table III
Risk factors for any infection, by cohort

Predictor	RR	*P* value	OR	*P* value
Overall cohort				
Injury in Mexico	1.27	.116	1.51	.051
Female	1.29	.004	1.44	.005
Pre-existing malignancy	1.60	.002	1.95	.006
Pre-existing cirrhosis	1.66	.005	2.38	.003
Matched cohort				
Injury in Mexico	1.43	.083	1.75	.063
Age	1.01	.021	1.02	.008
ISS ≥15	1.60	.068	1.02	.152
Days from injury to culture	1.02	.312	1.03	.312
Any ventilator days	1.58	.034	1.74	.113

RR, relative risk; *OR*, odds ratio.

between cohorts, Mexico patients had a higher rate of positive cultures (12.6% Mexico patients vs 7.9% US patients, $P = .035$), unlike in the overall study cohort (Table II). For infection site there was a trend toward the same results as the overall cohort, with more respiratory infections in Mexico patients and more urinary infections in US patients, but this no longer reached statistical significance. There was also no significant difference in types of organisms grown. Resistance profiles did remain significantly different however, with higher rates of ESBL *Klebsiella* (55.6% of all *Klebsiella* Mexico patients vs 0% US patients, $P = .013$) and overall gram-negative resistance (42.3% of *E. coli, Klebsiella, Pseudomonas* and *Acinetobacter* combined Mexico patients vs 0% US patients, $P < .001$). Of the 6 potentially resistant organisms specifically studied, the only resistance pattern identified in the matched set of US patients was MRSA, which was seen at a similar rate as in Mexico patients (38.9% Mexico patients vs 42.9% US patients, $P = .862$; Fig 3). Of all isolated organisms, resistant bacteria (ESBL *E. coli* and *Klebsiella*, MRSA, VRE, and MDR *Pseudomonas* and *Acinetobacter*) remained significantly more common in Mexico patients (26.9% of all organisms grown vs 8.1% US, $P = .010$).

For the matched cohort, logistic regression identified slightly different risk factors for infection than in the overall cohort, with increasing age the most significant predictor followed by injury in Mexico (Table III). Days from injury to culture, ISS and any ventilator days were included in the model, but were not statistically significant in final logistic regression. Assessment of risk factors for resistant infections was limited by the small number of patients in this cohort, so full logistic regression could not be performed; however, injury in Mexico and days from injury to culture remained significant on bivariate analysis (Table IV). Given that these were the same patients from Mexico as in the full cohort, the unique risk factor of tracheostomy placement in Mexico remained significant as well.

Discussion

We found that patients transferred to a United States trauma center after initial treatment in Mexico were more likely to harbor resistant organisms when infections were present, including a higher prevalence of resistance amongst gram-negative organisms. This was identified both in the overall cohort of patients assessed for infections in the first 3 days of US hospitalization, as well as in a cohort matched by time from injury to culture. The matched cohort also demonstrated a higher rate of overall infections in patients from Mexico, although this was not significant in the full cohort. These findings raise clinical concern that patients initially treated in Mexico may require a different regimen of empiric antibiotics while awaiting culture results than those treated only in the United States.

Table IV
Risk factors for resistant infection, by cohort

Predictor	RR	*P* value	OR	*P* value
Overall cohort				
Injury in Mexico	3.92	<.001	1.74	.305
Pre-existing smoking	3.32	<.001	3.52	.001
Trach placed prior to arrival	16.32	.001	9.30	.014
≥2 days injury before admission	4.79	<.001	2.88	.046
Matched cohort				
Injury in Mexico	5.00	.018		
Age	0.99	.670		
ISS ≥15	1.89	.520		
Days from injury to culture	1.08	<.001		
Any ventilator days	1.06	.921		
Mexico patients only				
Central line placed in Mexico	6.09	.013	—	NS
Foley placed in Mexico	4.22	.049	5.08	.081
Trach placed in Mexico	9.00	.005	18.68	.008
Any antibiotics given in Mexico	5.23	.014	4.37	.071

RR, relative risk; *OR*, odds ratio.
Unable to perform logistic regression on matched cohort due to low number of infections in US patients.

We found it particularly striking that all ESBL *Klebsiella* infections identified came from Mexico, with no cases identified during the studied timeframes in patients injured in the United States. The rate of ESBL *Klebsiella* was also higher than previously suggested in the literature,[8] although it is unclear if this is due to ongoing selection for resistant organisms or only regional variance.

In the overall cohort, of the potentially resistant organisms on which we focused Mexico patients most commonly grew *S. aureus* while *E. coli* was most common in US patients, although this distinction was not present in the matched cohort. We theorize that this was due in part to the differences in infection source in the overall cohort, with urinary tract infections being overwhelmingly common in patients from the United States. Given the timing of cultures (in the first 3 days of admission) these were likely urinary tract infections present at the time of admission. Body site infections, including at prior procedure and surgical sites, were more common in Mexico patients and likely contributed to the higher rates of *Staphylococcus* infection. Prior literature has shown higher rates of MRSA in the United States, including a study by Rivera et al comparing El Paso, Texas, and Ciudad Juarez, Mexico.[13] Though MRSA was the only resistant organism identified in US patients in the matched cohort, the prevalence was not significantly different than that seen in Mexico patients. As above this result differs from prior studies. Whether this is regional variance or changes in resistance patterns over time will require additional study.

Although the overall cohort represents the organisms present in the patient at the time of or shortly after admission to our facility (the first 3 days), Mexico patients present a median of 2 days after their injury, during which time they had some contact with the Mexico healthcare system. This raises potential bias in that Mexico patients may have hospital acquired organisms while US patients generally presented the day of their injury, and thus have community or skilled nursing facility acquired organisms depending on their location of residence. To counter this bias, we performed the matched cohort analysis, which matched patients in a 1:1 Mexico-to-US ratio, with the primary criteria being days from injury to culture; the same 3-day window after injury was then studied in both cohorts. Despite the fact that this matching changed the US cohort to include patients who had been hospitalized a similar amount of time, and who were thus at risk of harboring organisms acquired in our facility, we identified no resistant organisms in these US patients other than the MRSA identified above, making the difference with Mexico patients markedly important.

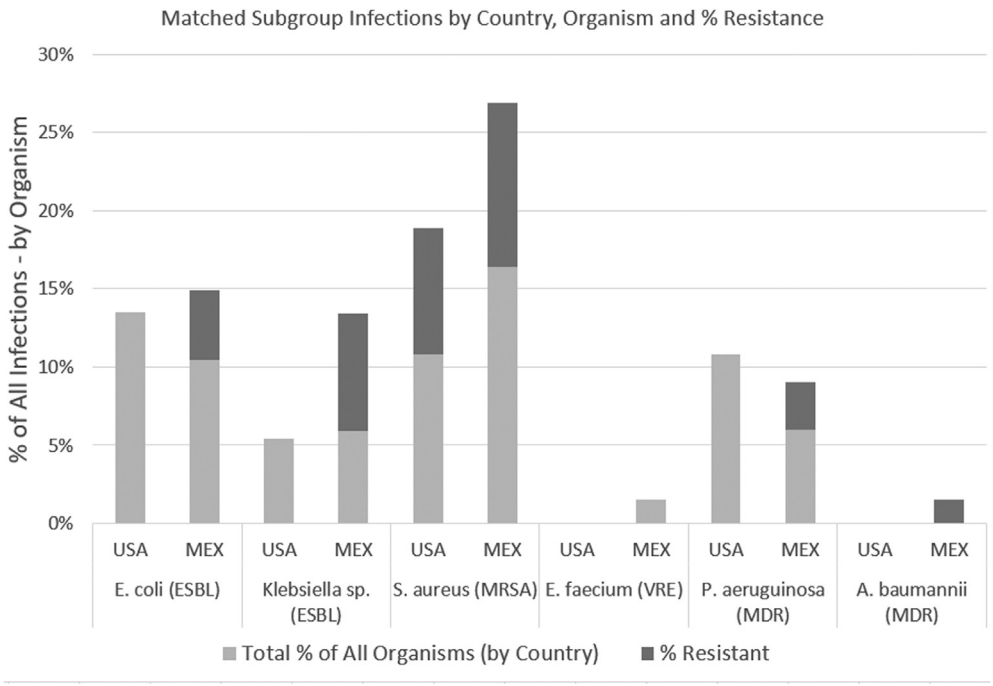

Fig 3. United States versus Mexico culture results by organism and percentage of each organism that was resistant, for the matched cohort. Types of resistance indicated with each organism.

One question raised by prior studies is whether patients treated abroad should be screened for DR organisms on hospital admission. Several centers have advocated screening for patients treated in either an inpatient or outpatient setting abroad at any time during the 12 months prior to hospitalization, regardless of the country of initial care.[2,9] The screening is intended to detect colonization with DR organisms, which may place the patient at higher risk of DR infection and may facilitate the spread of DR organisms to other patients. Screening protocols vary, with one study advocating rectal swabs for carbapenemase-producing *Enterobacteriaceae* and vancomycin-resistant *Enterococcus*[2] while another described nasal, inguinal, and rectal swabs as well as cultures of any wounds, lesions, or indwelling tubes (tracheostomy, urinary catheter, surgical drain, etc).[9] Although the screening protocols identified that up to 18% of patients were colonized with DR organisms,[9] differences in outcomes have not been described. Such screening protocols would be difficult in border regions such as ours as a high percentage of patients would be affected, and data on what precautions or treatment are appropriate for colonized patients are lacking. It is also unclear how often the colonization leads to true infection later. Our study did identify injury in Mexico, duration of time after injury, placement of tracheostomy in Mexico, and prior antibiotic administration as potential risk factors for resistant infection. Injury in Mexico, duration of time after injury and tracheostomy placement in Mexico persisted as risk factors for resistant infection even in bivariate analysis of patients matched for both time from injury to culture and placement of a tracheostomy prior to culture collection. There were 6 Mexico patients with a tracheostomy in place at the time of arrival to our facility, with times from injury to admission ranging from 8 to 35 days (median 16). Of these 6 patients, 4 were diagnosed with VAP within 3 days of their admission. Three of these patients grew resistant organisms, including 1 with ESBL *Klebsiella*, 1 with MRSA, and 1 with combination ESBL *E. coli*, MRSA, and MDR *Pseudomonas* from a single bronchoscopy specimen. Additional study will be needed to determine if screening in this subpopulation is cost effective.

This last point is particularly relevant in our setting, as many of our patients commute back and forth across the border on a weekly if not daily basis, making classification and risk stratification difficult. Even when patients are known to have been treated in a Mexico healthcare facility for their present injuries, there is often minimal data available regarding their prior care, including duration of hospital admission, details of operative procedures, antibiotic use, and culture results. As an example, we did attempt to examine antibiotic exposure prior to transfer in Mexico patients as reported above; however, these data were not available for the majority of patients. Where records were available patients often received multiple antibiotics, with a high prevalence of drugs that are often restricted in the United States, including amikacin and meropenem. We were unable to ascertain why these antibiotics were chosen: whether patients were known to have resistant organisms while still in Mexico, or the antibiotics chosen were used because of baseline high resistance levels in their facility, or due to poor antibiotic usage education or stewardship is unknown. Elucidating these issues will take additional investigation.

One policy change that may be beneficial and more easily implemented than screening or improving medical records available upon transfer is reassessment of an empiric antibiotic regimen for Mexico patients. Gram-negative organisms in Mexico patients showed high levels of resistance (>30%) to commonly utilized empiric antibiotics, including ceftriaxone, cefepime, gentamicin, and piperacillin-tazobactam, while sensitivity to ertapenem and meropenem was similar to US patients. Empiric carbapenem use may be appropriate in patients with multiple risk factors for resistance, such as prior antibiotics or procedures done in Mexico, and signs of a severe potentially gram-negative infection. Resistance patterns will then need to be followed over time to assess for the ongoing appropriateness of this regimen and to ensure it does not breed further resistance.

This study highlights the role of societal factors, including antibiotic stewardship, in the prevention of antibiotic resistance. The close proximity of San Diego and Tijuana effectively removes

any geographic effects on the resistance patterns identified, leaving differences in healthcare policy and antibiotic use to explain the variation seen in our patients. From a healthcare systems perspective, multifaceted interventions combining patient and public education, physician education, and restrictions on some antibiotics are most likely to be effective.[14–16] One issue that sets many developing countries apart from the United States is that of antibiotic availability without a prescription, which bypasses all attempts at physician education or restriction. The Mexico Ministry of Health attempted to address this problem in 2010, issuing a decree enforcing prior regulations that required prescriptions for human antibiotics. Regulations requiring pharmacies to retain and register prescription data have been poorly enforced, and there was an associated significant increase in retail pharmacies hiring general practitioners to provide consultations and prescriptions[6,17] despite concerns about the conflict of interest inherent in prescribing and dispensing in the same establishment.[18] Overall, antibiotic sales have decreased since the decree, but with most of the effect limited to penicillin and no statistically significant change in other antibiotic classes.[19] Additional changes on a national level, including surveillance and outcome tracking, are likely needed.

Our study does possess several limitations. Due to the retrospective nature of the study, and the limited 3-day windows assessed to avoid analyzing organisms that Mexico patients acquired after admission to our hospital, we were unable to track the spread of any resistant organisms from one cohort to another. We also did not assess initial antibiotic treatment for the identified infections, or measure any delays in appropriate antibiotic therapy due to antibiotic resistance. Despite the large number of patients passing through the international border each day, our study may also be underpowered to detect some risk factors for resistant infection. As an example, there were several variables in the multivariate analysis that only trended toward statistical significance despite being clinically relevant, such as prior antibiotic exposure. This was more prevalent in the matched cohort, with a much smaller number of US patients further limiting study power. Lack of medical records from Mexico detailing prior treatment for these patients is a significant limitation to their ongoing care in addition to hindering assessment of risk factors for infection. Finally, other studies described high rates of DR organism colonization in patients treated in another country $\leq$12 months prior to admission. We did not assess US patients for exposure to the healthcare system in Mexico (or any other country) at any timepoint other than for the present traumatic injury. This may have led to patients counted in the US cohort actually being colonized with bacteria acquired during prior trips to Mexico; however, if anything, this would decrease the difference in results between the two cohorts rather than accentuate it.

In conclusion, patients admitted to a US trauma center after initial treatment in Mexico are at high risk of infection with antibiotic-resistant organisms, particularly gram-negative infections, and may not be successfully treated by standard empiric antibiotic protocols. This difference in resistance patterns is marked despite close geographic proximity between treatment facilities in the US and Mexico. Ongoing global initiatives to improve antibiotic stewardship will be critical to limit the continued rise in drug-resistant infections.

Conflict of interest

The authors have indicated that they have no conflict of interest regarding the content of this article.

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