High mortality from blood stream infection in Addis Ababa, Ethiopia, is due to antimicrobial resistance: an observational cohort study.

Teshale Seboxa, Wondwossen Amogne, Workabeba Abebe, Tewodros Tsegaye, Aklillu Azazh, Workagegnhu Hailu, Kebede Fufa, Ayelign Derebe, Nils Grude, Thor-Henrik Henriksen.
Antibiotic timeline

CID 2013; 56(9):1310-18
Why is resistance a concern?

- Leads to treatment failures (of otherwise treatable infections).
- Leads to increased healthcare costs.
- Leads to increased societal costs (loss of income mostly).
- Resistance can spread (community effect is even greater than individual effect).
## Risk of Death is Higher in Patients Infected with Resistant Strains

| Outcome (number of studies included) | Resistant | Not resistant | RR (95% CI) |
|-------------------------------------|-----------|--------------|-------------|
| **Escherichia coli resistant to:**  |           |              |             |
| 3rd gen. cephalosporins             | 23.6      | 12.6         | 2.02 (1.41 to 2.90) |
| Fluoroquinolones                    | 0         | 0            |             |
| **Klebsiella pneumoniae resistant to:** |           |              |             |
| 3rd gen. cephalosporins             | 20        | 10.1         | 1.93 (1.13 to 3.31) |
| Carbapenems                         | 27        | 13.6         | 1.98 (0.61 to 6.43) |
| **Staphylococcus aureus resistant to:** |           |              |             |
| Methicillin (MRSA)                  | 26.3      | 16.9         | 1.64 (1.43 to 1.87) |

Antimicrobial Resistance
Global Report on Surveillance 2014
Table A3.2 Complete overview of findings addressing the question: *Does the published scientific literature indicate that there is an inferior outcome in infections caused by the following bacteria if they are resistant to the following antibacterial drugs?*

| Parameter                        | *E. coli* | Fluoroquinolones | *K. pneumoniae* | Carbapenems | Beta-lactam antibiotics (MRSA) |
|----------------------------------|-----------|------------------|------------------|-------------|-------------------------------|
| **3rd generation cephalosporins** |           |                  |                  |             |                               |
| All-cause mortality             | Yes (n = 16) | Yes (n = 8)      | Yes (n = 14)     | Yes (n = 11) | Yes (n = 107)                 |
| Bacterium-attributable mortality | Yes (n = 4) | No (n = 1)       | Yes (n = 4)      | No (n = 1)  | Yes (n = 46)                  |
| 30-day mortality                | Yes (n = 11) | Yes (n = 5)      | Yes (n = 7)      | Yes (n = 3) | Yes (n = 16)                  |
| Intensive care mortality         | ND         | ND               | ND               | No (n = 1)  | Yes (n = 5)                   |
| LOS in hospital                  | No (n = 3) | No (n = 3)       | No (n = 9)       | Unclear (n = 3) | Yes (n = 50)             |
| Admission to ICU                 | No (n = 1) | Yes (n = 1)      | Yes (n = 3)      | ND          | No (n = 17)                  |
| LOS in ICU                       | ND         | ND               | ND               | No (n = 1)  | Yes (n = 21)                 |
| Progression to septic shock      | ND         | Yes (n = 1)      | No (n = 3)       | ND          | Yes (n = 21)                 |
| Postinfection LOS                | No (n = 3) | ND               | Yes (n = 4)      | No (n = 1)  | Yes (n = 27)                 |
| Transfer to other health-care facility | ND | ND              | ND               | No (n = 1)  | Yes (n = 1)                   |
| Transfer to long-term care facility | ND | ND              | ND               | Unclear (n = 1) | Yes (n = 1)             |
| Attributable readmission         | ND         | ND               | ND               | ND          | No (n = 6)                   |
| Attributable mechanical ventilation | ND       | ND               | ND               | No (n = 1)  | No (n = 14)                  |
Does ABR lead to inferior outcomes? YES

Table A3.2 Complete overview of findings addressing the question: Does the published scientific literature indicate that there is an inferior outcome in infections caused by the following bacteria if they are resistant to the following antibacterial drugs?

| Parameter                        | E. coli          | K. pneumoniae     | S. aureus         |
|----------------------------------|------------------|-------------------|-------------------|
|                                  | 3rd generation cephalosporins | Fluoroquinolones | 3rd generation cephalosporins | Carbapenems | Beta-lactam antibiotics (MRSA) |
| All-cause mortality              | Yes (n = 16)     | Yes (n = 8)       | Yes (n = 14)      | Yes (n = 11) | Yes (n = 107)                 |
| Bacterium-attributable mortality | Yes (n = 4)      | No (n = 1)        | Yes (n = 4)       | No (n = 1)   | Yes (n = 46)                  |
| 30-day mortality                 | Yes (n = 11)     | Yes (n = 5)       | Yes (n = 7)       | Yes (n = 3)  | Yes (n = 16)                  |
| Intensive care mortality         | ND               | ND                | ND                | No (n = 1)   | Yes (n = 5)                   |
| LOS in hospital                  | No (n = 3)       | No (n = 3)        | No (n = 9)        | Unclear (n = 3) | Yes (n = 50)                 |
| Admission to ICU                 | No (n = 1)       | Yes (n = 1)       | Yes (n = 3)       | ND           | No (n = 17)                   |
| LOS in ICU                       | ND               | ND                | ND                | No (n = 1)   | Yes (n = 5)                   |
| Progression to septic shock      | ND               | Yes (n = 1)       | No (n = 3)        | ND           | Yes (n = 21)                  |
| Postinfection LOS                | No (n = 3)       | ND                | Yes (n = 4)       | No (n = 1)   | Yes (n = 27)                  |
| Transfer to other health-care facility | ND           | ND                | ND                | No (n = 1)   | Yes (n = 1)                   |
| Transfer to long-term care facility | ND            | ND                | ND                | Unclear (n = 1) | Yes (n = 1)                 |
| Attributable readmission         | ND               | ND                | ND                | ND           | No (n = 6)                    |
| Attributable mortality           | ND               | ND                | ND                | ND           | No (n = 14)                   |
E. coli resistance in Ethiopia

- 53% of strains R to ceftazidime
- 70% of strains R to ceftriaxone
- 71% of strains R to fluoroquinolones

Based on national data submitted to WHO – ? denominator

WHO report on ABR 2014
Klebsiella and other GNB: Resistance in Ethiopia

- **Klebsiella:**
  - 14% of strains R to ceftazidime
  - 20% of strains R to ceftriaxone
  - No data for Carbapenems (imipenem)

- **Shigella:**
  - 0 - 9.2% of strains R to Fluoroquinololones

- **Non-typhoidal Salmonella:**
  - 14% of strains R to FQ

WHO report on ABR 2014

June 2015 ESIM oral presentation
MRSA in Ethiopia

- 31.6% of *S. aureus* strains are R to Methicillin
- Comparisons:
  - Canada: 21% of strains are MRSA
  - USA: 51% of strains are MRSA
  - Netherlands: 1.4% of strains are MRSA

WHO report on ABR 2014
Summary Ethiopian data

• National data submitted to WHO suggest:
  – High rates of R to cephalosporins and FQ among common G(-) bacteria
  – High rates of methicillin resistance among S. aureus (MRSA)

• BUT:
  – Questions re. methods used to measure R
  – Data may be skewed towards urban hospitalized patients, and denominators are low
  – Resistance rates may be overestimated – which can lead to prescription of broader spectrum AB and worsening of the problem!
The study objectives:

1. Bacteremia as predictor of mortality?
2. Antimicrobial sensitivity vs. survival?
3. G(-) resistance to 3rd gen cephalosporins?
4. Distribution of antimicrobial resistance?
   Any co-variations?
Materials & methods
Study groups

Three different groups from Oct 2012 - Sept 2013.

**Group 1**: Adults pts (> 18 yrs) admitted at Tikur Anbessa Hospital with clinical suspicion of septicemia.

**Group 2**: Blood culture from peds and adult cases admitted with clinical suspicion of septicemia at Yekatit 12 Hospital Medical College.

**Group 3**: Blood culture (+) Peds cases admitted at Tikur Anbessa Hospital.
### Study design:

| Study design            | Group 1            | Group 2            | Group 3            |
|-------------------------|--------------------|--------------------|--------------------|
|                         | Case series,       | Case series,       | Case series,       |
|                         | prospective        | prospective        | Cross-sectional    |
| Out comes               | Discharge/Death    | Discharge/Death    | Culture result     |
|                         | Culture result     | Culture result     |                    |
| Blood culture           | Aerobic &          | Aerobic &          | In house           |
|                         | anaerobic (Bactec) | anaerobic (Bactec) | method             |
|                         |                    |                    |                    |
| Number /Total           | 299                | 107                | 166 = 572          |

**Notes:**
- June 2015 ESIM oral presentation
- 9/15/2015
Study methods

• Blood cultures were collected with Bactec aerobic and anaerobic blood culture bottles plus in house method.
• Negative sample= No growth with in 5 days of incubation.
• Samples were kept for 10 days in Endocarditis suspects.
• Sensitivity evaluated for antimicrobial agents used in Ethiopia except carbapenems.
• Sensitivity testing was performed with Kirbauer’s method.
Study criteria for Group 1 & 2

**Inclusion criteria:**
Clinical suspicion of septicemia or septic shock plus any 2 of the following.

1. Axillary $T^0$: $> 38.5^0C$ or $< 36.5^0C$.
2. Heart rate $> 90$ beats/min
3. RR $> 20$ breaths/min
4. WBC $> 12K$, $< 4K$, or $> 10\%$ bands.

**Exclusion criteria:**
1. Antimicrobial therapy within the last 72 hrs.
2. No consent
Results (Group 1)
## Baseline characteristics

| Variable                        | Frequency | Percentage |
|---------------------------------|-----------|------------|
| Age (Mean ± SD)                 | 32 (16)   |            |
| Sex (M:F)                       | 155:144   | 1.1:1      |
| **Departments**                 |           |            |
| Medical                         | 168 (56.2%) | 168 (56.2%) |
| Emergency                       | 128 (42.8%) | 128 (42.8%) |
| Surgical                        | 2 (0.7%)   | 2 (0.7%)   |
| Gyne-obs                        | 1 (0.3%)   | 1 (0.3%)   |
| Prior antimicrobials             | 74        | 24.7%      |
| Mean hospital days (± 1SD)      |           |            |
| Medical                         | 9 (14)    |            |
| Emergency                       | 1.6 (1.7) |            |
| Surgical                        | 9 (7)     |            |
| Gyne-obs                        | 1 (1)     |            |
## Baseline characteristics of mortality & survivor cases

| Variable                                                | Mortality | Survivors |
|---------------------------------------------------------|-----------|-----------|
| Frequency                                               | 44        | 255       |
| Female: Male                                            | 20:24     | 124:131   |
| Age (Median/Range)                                     | 25 (13-70)| 28 (13-98)|
| Number of days within the hospital before blood culture (median) | 2         | 2         |
| Hgb < 7 gms /dL                                        | 17        | 52        |
| ANC < 0.5 K                                             | 9         | 20        |
| Platelets < 20 K                                       | 20        | 25        |
| HIV status (+)                                          | 3         | 41        |
| Recent IV antibiotics (Yes)                            | 8         | 30        |
## Clinical diagnosis

| Diagnosis                  | Number ( % total)   |
|----------------------------|--------------------|
| **Hematology:**            |                    |
| 1. acute leukemia          | 53 (17.7%)         |
| 2. pancytopenia            | 21 (7%)            |
| 3. Others                  | 13 (14.9%)         |
| Total                      | 87 (29.1%)         |
| **Cardiac:**               |                    |
| Infective endocarditis     | 55 (18.4%)         |
| **HIV/AIDS +**             | 38 (12.7%)         |
| **Sepsis +**               | 34 (11.4%)         |
| **Others**                 | 85 (28.4%)         |
| **Total**                  | 299                |
## Number of Positive culture samples

| Bacteria        | Medical | Emergency | Gyne obs | Surgical | Total |
|-----------------|---------|-----------|----------|----------|-------|
| E. coli         | 9       | 7         | 0        | 0        | 16    |
| CoNS            | 9       | 2         |          |          | 11    |
| S. aureus       | 3       | 4         |          |          | 7     |
| Salmonella sp.  | 2       |           |          |          |       |
| Klebsiella sp.  | 1       |           |          |          |       |
| C. braakii      | 1       |           |          |          |       |
| Bacteria              | Number ( %)   |
|----------------------|---------------|
| E. coli              | 16 (42.1%)    |
| CoNS                 | 11 (28.9%)    |
| S. aureus            | 7 (18.4%)     |
| Salmonella sp.       | 2 (5.3%)      |
| Klebsiella sp.       | 1 (2.6%)      |
| C. braakii           | 1 (2.6%)      |
| **Total**            | **38/299 (12.7%)** |
| Bacteria    | N | A/cla (n) | Cefo (n) | Ceftr (n) | Ceph (n) | Cipro (n) | Clin (n) | Ery (n) | Gen (n) | Nor (n) | Nit (n) | Sulf (n) | Van (n) |
|-------------|---|-----------|----------|----------|---------|----------|----------|--------|--------|--------|--------|---------|--------|
| **Gram +ves** |   |           |          |          |         |          |          |        |        |        |        |         |        |
| CoNS        | 11| 1         | 7        | 7        | 6       | 5        | 4        | 7      |        |        |        | 5       | 2      |
| S. aureus   | 7 | 0         | 1        | 2        | 1       | 2        | 0        | 0      | 0      | 0      | 0      | 5       | 0      |
| **Total Gm +ves** | 18| 1         | 8        | 9        | 7       | 5        | 6        | 7      | 3      | 3      | 2      | 10      | 2      |
| **Gram –ves** |   |           |          |          |         |          |          |        |        |        |        |         |        |
| E. coli     | 16| 11        | 10       | 9        | 11/15   | 8/15     | 12       | 3/7    | 12     |        |        |         |        |
| Salmonella sp| 2 | 0         | 0        | 0        | 0       | 0        | 0        | 0      | 0      |        |        |         |        |
| Klebsiella sp| 1 | 1         | 1        | 1        | 1       | 1        | 1        | 1      | 0      |        |        |         |        |
| C. braakii  | 1 | 0         | 0        | 0        | 0       | 0        | 0        | 0      |        |        |        |         |        |
| **Total Gm -ves** | 20| 9         | 9        | 9        | 8       | 9        | 12       | 12     |        |        |        |         |        |
### Resistant E. Coli (Medical wards vs. Emergency room)

|          | A/clav | Cefo | Ceftr | Cipro | Genta | Norfl |
|----------|--------|------|-------|-------|-------|-------|
| Med E. coli | 7/9    | 6/9  | 5/9   | 6/8   | 5/9   | 7/8   |
| Emer E. coli | 4/7    | 4/7  | 4/7   | 5/7   | 3/6   | 5/7   |
| Total     | 11/16  | 10/16| 9/16  | 11/15 | 8/15  | 12/15 |
## Resistant CoNS (Medical wards vs. Emergency room)

| CoNS | A/cla | Cefo | Ceft | Ceph | Clin | Ery | Sulfa | Van |
|------|-------|------|------|------|------|-----|-------|-----|
| Med  | 0/9   | 5/9  | 6/9  | 4/9  | 3/9  | 6/9 | 4/9   | 2/8 |
| Emer | 1/2   | 2/2  | 1/2  | 2/2  | 1/2  | 1/2 | 1/2   | 0/2 |
| Total| 1/11  | 7/11 | 7/11 | 6/11 | 4/11 | 7/11| 5/11  | 2/10|
### Blood culture result vs. mortality

|                | Discharged alive | Died in hospital | Total |
|----------------|------------------|------------------|-------|
| Culture (+)    | 21 (8%)          | 17 (39%)         | 38 (13%) |
| Culture (-)    | 234 (92%)        | 27 (61%)         | 261 (87%) |
| Total          | 255              | 44               | 299   |

**OR= 7.0 (95% CI 3.3 -14.9)**

10% of those who died & 80% of the survivors had *Enterobacteriaceae* sensitive to both ceftriaxone & cefotaxime.
## Death proportions vs. Charlson comorbidity index scores

| Comorbidity score | 0-1 | 2-3 | 4-5 | 6+ |
|-------------------|-----|-----|-----|----|
| Deaths            | 11  | 25  | 4   | 4  |
| No of patients    | 132 | 110 | 14  | 43 |
| % mortality       | 8.3 | 22.7| 28.6| 9.3|
Group 2
Yekatit 12 Hospital Medical College

- Age: 36 days – 50 years.
- Challenge: Most had taken antibiotics prior to 72 hrs.
- Culture technique: One sampling – 3 bottles each
- Positive culture: 2 patients - both positive by both methods.

| Sample | Organism         | Cefotaxime | Gentamycin |
|--------|------------------|------------|------------|
| M 8/12 | Citrobacter spp  | R          | S          |
| M 3    | E coli           | R          | R          |

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9/15/2015
## Distribution of species responsible for childhood sepsis, Tikur Anbessa Hospital

| Species                                | All   | Early onset (newborn) sepsis N=20 | Late onset (newborn) sepsis N= 14 | Age unknown N=15 | < 15 yrs but > 1 month N= 67 |
|----------------------------------------|-------|-----------------------------------|-----------------------------------|------------------|-------------------------------|
| Non-fermenters                         | 29    | 4                                 | 7                                 | 5                | 13                            |
| Klbsiella spp                          | 35    | 5                                 | 1                                 | 5                | 24                            |
| Non-Klebsiella enterobacteriaceae      | 31    | 7                                 | 1                                 | 5                | 18                            |
| S. aureus                              | 15    | 3                                 | 4                                 | 0                | 8                             |
| Enterococci                            | 1     | 1                                 | 0                                 | 0                | 0                             |
| Streptococcus spp                      | 4     | 0                                 | 0                                 | 0                | 4                             |
| Aspergillus spp                        | 1     | 0                                 | 1                                 | 0                | 0                             |

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Percent co-variation of resistant and sensitive isolates between ceftazidime and six other antibiotics.

|                | Non-Klebsiella Enterobacter | Klebsiella spp | Pseudomonas spp | Acientobacter spp | All  |
|----------------|------------------------------|----------------|-----------------|-------------------|------|
| Ceftaz         | R=18 S=11                    | R=29 S=5       | R=6 S=5         | R=11 S=7          | R=64 S=28 |
| Gent           | 83% 100%                     | 93% 20%        | 83% 100%        | 64% 100%          | 84% 85% |
| Chlor          | 44% 100%                     | 76% 75%        | 83% 20%         | 91% 72%           | 71% 74% |
| Tetra          | 89% 36%                      | 88% 60%        | 67% 80%         | 64% 67%           | 82% 56% |
| Co-tri         | 94% 73%                      | 83% 60%        | 50% 80%         | 80% 86%           | 82% 75% |
| Cipro          | 67% 100%                     | 31% 60%        | 0% 100%         | 45% 100%          | 39% 83% |
| Amik           | 8% 100%                      | 4% 60%         | 32% 50%         | 10% 100%          | 10% 81% |
Phenotypic betalactamases from TAH

• 17 consecutive ceftazidime-resistant isolates
• 16/17 carried ESBL-A, One was AmpC (+).
• One ESBL – A neg and amp-C neg.

This strain was meropenemase resistant.

(Before introduction of carbapenems in Ethiopia)
• 12.7% of blood cultures were positive (Group 1)

• G (+) : CoNS= 60%, S aureus= 40%,  G (-): E. coli=80%

• Anaerobic culture : No positives.

• E. coli & CoNS more in the medical wards, mean stay= 9 days vs. emergency room= 2 days.

• E. coli > 70% were resistant to 3rd generation cephalosporins, ciprofloxacin & Gentamycin( Previous study 90% were ESBL).
• In-hospital mortality from proven BSI is high.
• 10% of the mortality cases had *Enterobacteriaceae* sensitive to both ceftriaxone & cefotaxime.
• 2/3 of G(-) resistant to 3\textsuperscript{rd} generation cephalosporins were resistant to ciprofloxacin and gentamycin.
• Carbapenem resistance before its introduction.
• Amikacin seems a better option provided used rationally.
Thank You.