Acute care for the three leading causes of mortality in lower-middle-income countries: A systematic review

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ABSTRACT

According to the World Health Organization, the three leading causes of mortality in lower-middle-income countries (LMIC) are ischemic heart disease (IHD), stroke, and lower respiratory infections (LRIs), causing 111.8, 68.8, and 51.5 annual deaths per 100,000, respectively. Due to barriers to healthcare, patients frequently present in critical stages of these diseases. Measured implementations in critical care in LMIC have been published; however, the literature has not been formally reviewed. We performed a systematic review of the literature indexed in PubMed as of October 2017. Abstracts were limited to human studies in English, French, and Spanish, conducted in LMIC, and containing quantitative data on acute care of IHD, stroke, and LRI. The search resulted in 4994 unique abstracts. Through multiple rounds of screening using criteria determined a priori, 161 manuscripts were identified: 38 for IHD, 20 for stroke, 26 for adult LRI, and 78 for pediatric LRI. These studies, predominantly from Asia, demonstrate successful diagnostic and treatment measures used in providing acute care for patients in LMIC. Given that, only four manuscripts originated in Central or South America, original research from these areas is lacking. IHD, stroke, and LRI are significant causes of mortality, especially in LMIC. Diagnostic and therapeutic interventions for IHD (monitoring, medications, thrombolytics, percutaneous intervention, coronary artery bypass graft), stroke (therapeutic hypothermia, medications, and thrombolytics), and LRI (oxygen saturation measurement, diagnostic ultrasound, administration of oxygen, appropriate antibiotics, and other medications) have been studied in LMIC and published.

Key Words: Acute care, critical care, ischemic heart disease, lower-middle-income countries, lower respiratory infection, stroke

INTRODUCTION

According to the World Health Organization (WHO), the three leading causes of mortality in lower-middle-income countries (LMIC) are ischemic heart disease (IHD), stroke, and lower respiratory infections (LRIs), causing 111.8, 68.8, and 51.5 annual deaths per 100,000, respectively. The 2010 Global Burden of Disease (GBD) Study indicated that IHD is the leading cause of mortality and loss of disability-adjusted life years (DALYs) worldwide, accounting for roughly seven million deaths and 129 million DALYs annually. Noncommunicable disease processes have been a leading cause of death in high-income countries for decades. However, the previous focus in LMICs has been on communicable diseases and now there is an aging population thought to account for a shift to noncommunicable disease deaths.
For example, there have been great improvements in the age-adjusted mortality rates associated with IHD over the past two decades; however, rates in high-income countries are largely accountable for this improvement and rates in the LMIC remain largely unchanged.\[^{4}\] There have been efforts to decrease mortality in LMIC including communicable and noncommunicable diseases, but they have been primarily focused on preventative methods (clean water, environmental safety measures, safe sexual practices, and prenatal care).\[^{5,6}\] Some research suggests that this mortality can be decreased with effective, focused, and evidence-based acute care. Seven out of the top 15 causes of morbidity and mortality worldwide can be reduced through the provision of high-quality, cost-effective emergency care.\[^{7}\] Delving further, on account of the epidemiologic transition and concurrent decreased access to health care, patients often present in later-stage forms of illness and require more acute interventions. As a result, there must be a greater emphasis on acute care for noncommunicable diseases. A recent systematic review identified quantitative data on the delivery of emergency care in LMICs.\[^{8}\] Our literature review aims to present updated specific quantitative data for the acute care of the 2015 three leading causes of death in LMIC.

### METHODS

**Systematic search and selection criteria**

We performed a systematic review of the literature indexed in PubMed as of October 2017. Abstracts were limited to human studies in English, French, and Spanish. We used a comprehensive list of terms [Appendix A], including “Critical Care,” “Critical Illness,” “Emergency Medicine,” “Acute Disease,” “Ischemic Heart Disease,” “Cerebrovascular Disorders,” “Lower Respiratory Tract Infections,” and other similar terms along with individual names of LMICs according to the World Bank.\[^{9}\] The initial search returned 5349 titles; 355 were duplicates that were excluded before review. On primary review of the remaining 4994 abstracts, 4265 were excluded by two reviewers (with conflicts resolved by a third) using the following a priori exclusion criteria: Not human; not in English/French/Spanish; not in LMIC; not a complete manuscript (e.g., only an abstract, poster presentation, lecture, letter, or short communication); not conducted in a LMIC – as defined by the World Bank classification of countries as of October 27, 2015, as the search was initially done in November 2015 and then updated in October 2017; and a manuscript without a focus on the acute care of IHD, stroke, or LRI. The abstracts of the remaining 729 manuscripts were screened by two reviewers (with conflicts resolved by a third); 127 were excluded based on inability to retrieve the manuscript. The remaining 602 manuscripts were reviewed by two reviewers, with conflicts resolved by a third, for the following inclusion criteria: manuscripts with a primary focus on or detailed section including specific acute care interventions for IHD, stroke, and LRI. Data were then extracted from the 161 manuscripts identified. All screening and data extraction were completed using Microsoft Excel. The study institution did not require the Institutional review board approval, as this was a review limited to the existing literature.

### RESULTS

The search produced 5349 titles of interest, of which 161 manuscripts were selected for full-text analysis in this review: 38 IHD, 20 stroke, 26 adult LRI, and 77 pediatric LRI [Figure 1].

#### Ischemic heart disease

Within the IHD subgroup, articles were primarily from Asia (19), the Middle East (9), and Eastern Europe (8), with only one from Africa and one from South America. Articles focused on outcomes after cardiopulmonary resuscitation, medications, thrombolytics, percutaneous coronary intervention, coronary artery bypass graft (CABG), intra-aortic balloon pump (IABP), and other interventions [Table 1].

#### Diagnosis

Acute coronary syndrome (ACS) carries the risk of mortality in the acute setting, and survivors carry the risk of recurrent ACS or developing chronic heart failure and reduced exercise tolerance, representing significant DALYs. Diagnosis of ACS requires an electrocardiogram (EKG) machine and the expertise to interpret the symptoms of the patient and the EKG and to know the indication and contraindications of various therapeutic agents. Diagnosis and treatment for ACS do

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**Figure 1:** Flowchart of the systematic review process (PRISMA diagram)
Table 1: Acute coronary syndrome articles included

| Author          | Region       | Country     | Year | Title                                                                 | Findings                                                                                                                                                                                                 |
|-----------------|--------------|-------------|------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CPR             | Asia         | Thailand    | 2006 | Outcome of cardiopulmonary resuscitation in a 2300-bed hospital in a developing country | Retrospective (n=639). Survival to discharge rate after in-hospital cardiac arrest is 6.9%. Initial survival rate was strongly associated with being in a monitored area. Defibrillators and critical care areas were insufficient. |
| Singh RB        | Asia         | India       | 1998 | Effect of treatment with magnesium and potassium on mortality and reinfarction rate of patients with suspected acute MI | Prospective RCT (n=326). Magnesium and potassium infusion immediately after acute MI may lead to reduction in complications and 2-year mortality.                                                                 |
| Kaul UA         | Asia         | India       | 1988 | Early intervention with propranolol after acute MI: serial left ventricular function determined by M-mode and cross-sectional echocardiography | Prospective RCT (n=50). LVEF significantly improved in patients with acute MI after early intervention with propranolol (69% vs. 52%, P<0.001)                                                                 |
| Karim MA        | Asia         | Sri Lanka   | 1995 | Thrombolytic therapy in acute MI in Pakistan                          | Retrospective (n=194). A statistically significant reduction in mortality was seen in the group that received streptokinase (15.2%) compared to those who did not receive SK (24.7%), (P= <0.05)                                      |
| Kaul U          | Asia         | India       | 1998 | Outcomes of primary stenting for acute MI                             | Prospective (n=76). Primary stenting is safe and feasible in the majority of patients with good short-term outcome.                                                                                         |
| Constantine GR  | Asia         | Sri Lanka   | 1999 | Management of acute MI in general medical wards in Sri Lanka          | Retrospective (n=259). Complications were less common among patients who received streptokinase.                                                                                                          |
| Okuyan E        | Eastern Europe| Turkey      | 2010 | Caring of ST‑elevation MI patients in rural community hospital settings: Determinants of in-hospital mortality          | Retrospective (n=559). Improvement ofprehospital fibrinolysis capabilities should decrease mortality.                                                                                     |
| Abdel-Salam Z   | Middle East  | Egypt       | 2010 | The modified Selvester QRS score: Can we predict successful ST segment resolution in patients with MI receiving fibrinolytic therapy? | Prospective (n=60). The selvester QRS score can reliably predict adequate ST segment resolution in patients with first acute STEMI receiving fibrinolytic therapy, with a high sensitivity and an acceptable specificity |
| Taheri L        | Middle East  | Iran        | 2015 | Effect of streptokinase on reperfusion after acute MI and its complications: An ex-postfacto study | Retrospective (n=300). Patients who received thrombolytics had reduced mortality and reduced incidence of arrhythmia compared with patients who did not receive thrombolytics. |
| PCI             | Asia         | India       | 2000 | Reversal of slow flow phenomenon during primary stenting by bail-out administration of abciximab | Prospective (n=131). Patients who had been administered Abciximab intravenously had lower mortality than patients with persistent slow flow (1.8% vs. 33%, P<0.001) at 30-day follow-up |
| Alidoosti M     | Middle East  | Iran        | 2007 | Outcomes of primary percutaneous coronary intervention in AMI at Tehran heart center | Prospective (n=83). Primary angioplasty was successful in 95% of cases.                                                                                                                                  |
| Jafary FH       | Middle East  | Pakistan    | 2007 | Outcomes of primary percutaneous coronary intervention at a joint commission international accredited hospital in a developing country -- can good results, possibly similar to the west, be achieved? | Retrospective (n=277). Procedural success was 97%.                                                                                                                                                      |
| Karabay KO      | Eastern Europe| Turkey      | 2011 | Percutaneous revascularization of total or subtotal left main occlusion in the setting of acute MI | Retrospective (n=8). Percutaneous coronary intervention in patients with left main coronary occlusion complicated by acute MI is feasible and effective, and offers a good mid-term outcome for hospital survivors. |
| Farman MT       | Middle East  | Pakistan    | 2011 | Outcome of primary percutaneous coronary intervention at public sector tertiary care hospital in Pakistan | Prospective (n=113). Optimal results of primary percutaneous coronary intervention can be achieved for acute STEMI in a developing country at a tertiary care public sector hospital. The results are comparable and nearly similar to the west. |

Contd...
| Author       | Region         | Country   | Year | Title                                                                 | Findings                                                                                                                                                                                                 |
|--------------|----------------|-----------|------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kirm C       | Eastern Europe | Turkey    | 2011 | Primary angioplasty in a high-volume tertiary center in Turkey: in-hospital clinical outcomes of 1625 patients | Retrospective (n = 1625). Primary PCI is an effective method in achieving complete revascularization of the infarct-related artery. Successful in-hospital results not only depend on the experience and equipment of the center, but also on how rapidly reperfusion is achieved. |
| Subban V     | Asia           | India     | 2012 | Percutaneous coronary intervention in cardiogenic shock complicating acute ST-elevation MI — a single center experience | Retrospective (n = 41). Patients with better pre-procedure TIMI flow in the IRA had better survival (P = 0.0005). Successful PCI was achieved in 48.8% of patients. Patients with successful PCI had better short-term survival in comparison with patients with failed PCI (80% vs. 9.6%). Mortality remains high even with PCI. Achieving infarct-related artery patency with TIMI 3 flow is the main determinant of survival. Survival and functional status are good in patients who are discharged from hospital. |
| Dubey L      | Asia           | Nepal     | 2013 | Early clinical outcomes of primary percutaneous coronary intervention in Bhartapur, Nepal | Prospective study (n = 68). Primary percutaneous coronary intervention improves the early clinical outcomes in patient with acute STEMI. Despite having no onsite cardiac surgery backup, primary percutaneous coronary intervention was feasible with acceptable complications in a tertiary-care teaching hospital. |
| Dubey L      | Asia           | Nepal     | 2013 | Percutaneous coronary intervention without onsite cardiac surgery backup | Prospective study (n = 101). Percutaneous coronary intervention was feasible with acceptable complications in a tertiary-level hospital without onsite cardiac surgery backup. |
| Subban V     | Asia           | India     | 2014 | Outcome of primary PCI - an Indian tertiary care center experience    | Prospective (n = 672). Patients who underwent primary PCI for STEMI were observed. Median door-to-balloon time was 65 min. Overall in-hospital mortality was 4.2% but was 61.3% for patients with cardiogenic shock. |
| Victor SM    | Asia           | India     | 2016 | Two-year follow-up data from the STEPP-AMI study: A prospective, observational, multicenter study comparing tenecteplase facilitated PCI versus primary PCI in Indian patients with STEMI | Prospective (n = 200). Compared immediate thrombolysis followed by PCI in 3-24 h with primary PCI and found a nonsignificant trend towards better outcomes with primary PCI that disappeared at 2 years. |
| Jahic E      | Eastern Europe | Bosnia and Herzegovina | 2017 | Experience and outcomes of primary percutaneous coronary intervention for acute ST-segment elevation MI of tertiary care center in Bosnia and Herzegovina | Prospective (n = 549). By extending PCI availability, the tertiary care center achieved low door to balloon times and low mortality. Most access was through the radial artery. |
| Dubey G      | Asia           | India     | 2017 | Primary percutaneous coronary intervention for acute ST elevation MI: Outcomes and determinants of outcomes: A tertiary care center study from North India | Prospective (n = 371). Patients underwent PCI for ACS. Mortality was 66.7% for patients presenting in shock, but 12% overall. Mean door to balloon time was 51 min, with longer door to balloon time associated with higher mortality. 83% of the patients were male. |
| CABG         | Asia           | India     | 1999 | Myocardial revascularization after acute MI                           | Prospective (n = 129). CABG can be carried out with low risk following AMI in stable patients for postinfarct angina. |
| Dar MI       | Middle East    | Pakistan  | 2007 | Outcome of patients after coronary artery bypass grafting in cardiogenic shock | Retrospective (n = 412). CABG in cardiogenic shock produces significant 1-year survival benefits and improvements in functional class. Therefore, early surgical intervention is suggested where percutaneous coronary intervention is not possible or contraindicated for anatomical reasons. |
| Guney MR     | Eastern Europe | Turkey    | 2008 | Results of treatment methods in cardiac arrest following coronary artery bypass grafting | Retrospective (n = 148). Better short- and long-term results were observed in the re-revascularization group. |

Contd...
| Author       | Region       | Country       | Year | Title                                                                 | Findings                                                                 |
|--------------|--------------|---------------|------|-----------------------------------------------------------------------|--------------------------------------------------------------------------|
| Gurer O      | Eastern Europe | Turkey        | 2011 | Left anterior descending artery revascularization in low-risk patients: early outcomes after off-pump versus on-pump surgery | Retrospective (n=300). Performing CABG off-pump reduces costs but has similar outcomes for low risk patients with left main disease |
| Sheikh MR   | Middle East  | Pakistan      | 2015 | Outcome of coronary artery bypass grafting in a tertiary care center in Pakistan | Retrospective (n=2851) Patients treated with CABG for CAD. While over half of the patients had elective surgeries, the number includes patients who had emergent procedures or cardiogenic shock. Overall mortality was 6.5% in patients with left main disease and 2.6% in patients with multi-vessel disease |
| PCI vs. CABG | Perikhanyan A | Asia          | 2011 | Effectiveness and cost-effectiveness of coronary artery bypass surgery versus drug eluting stents in Armenia: A feasibility study | Prospective (n=142). CABG is a more cost-effective strategy than PCI with drug-eluting stent in terms of preventing RR, MI and death and saving costs |
| Sokullu O   | Eastern Europe | Turkey        | 2011 | Emergency management for critical left main coronary artery stenosis | Retrospective (n=108). Some centers use CABG as the first line therapy for critical left main stenosis and use PCI as a back-up for patients too critically ill to undergo surgery |
| Arso IA     | Asia         | Indonesia     | 2014 | In-hospital major cardiovascular events between STEMI receiving thrombolysis therapy and primary PCI | Retrospective (n=1311). Nonrandomized patients who presented with STEMI <12 h who received either thrombolysis (78) or primary PCI (53) showed no difference in-hospital major cardiovascular events or in-hospital mortality (10.3% vs. 9.4%; P=0.87). Primary PCI had lower incidence of heart failure |
| IABP        | Dharma S     | Indonesia     | 2013 | The use of intra-aortic balloon pump in a real-world setting: A Comparison between Survivors and Nonsurvivors from ACS Treated with IABP. The Jakarta ACS Registry | Retrospective (n=121). IABP appears to be safe and tended to be favorable in noncardiogenic shock ACS patients, particularly non-STE-ACS. A heart rate of >100 beats per minute prior to IABP insertion was the strongest predictor of 30-day mortality |
| Jafary FH    | Middle East  | Pakistan      | 2004 | Survival of patients treated with intra-aortic balloon counter pulsation at a tertiary care center in Pakistan - patient characteristics and predictors of in-hospital mortality | Retrospective (n=95). Despite high mortality among patients requiring IABC, 65.3% patients left the hospital alive, suggesting that IABC is a feasible therapeutic device, even in a developing country |
| OTHER        | Meostaghfir A | Africa, Morocco, Tunisia | 2012 | Management of ACSs in Maghreb countries: The ACCESS registry | Observational (n=1687). ACS patients from 3 Maghreb countries. The use of evidence-based pharmacological therapies for ACS was quite high. Factors associated with a lower risk of death were male sex (HR: 0.63, P=0.014) and PCI (HR: 0.25, P<0.001) |
| Kazmi WH     | Middle East  | Pakistan      | 2012 | Noninvasive therapy for the management of patients with advanced coronary artery disease | Prospective (n=43). CSWT application to the ischemic myocardium in patients with refractory angina pectoris improved symptoms and reduced the severity of ischemic areas at 6 months after CSWT treatment compared with the baseline. No side effects were observed with this therapy |
| de Andrade L | South America | Brazil        | 2014 | System dynamics modeling in the evaluation of delays of care in ST-segment elevation MI patients within a tiered health system | Mixed methods. 29 STEMI patients were transferred to PCI center which accepted the patients after remotely reviewing ECG. The average delay from seeing provider to obtaining ECG was 28 min, to having ECG reviewed at PCI center was 75 min, and 78 minutes awaiting transfer. The analysis identified issues with personnel, equipment, and logistics setups leading to delays |
Table 1: Contd...

| Author    | Region | Country | Year | Title                                                                 | Findings                                                                 |
|-----------|--------|---------|------|----------------------------------------------------------------------|--------------------------------------------------------------------------|
| Dahn et al.: Acute care for top 3 causes of death in LMIC | Asia    | India   | 2014 | eICU reduces mortality in STEMI patients in resource-limited areas  | Retrospective. Cardiologist remotely supported a hospital in the evaluation of patients with chest pain, including reviewing EKGs and making recommendations regarding thrombolitics. The 30-day mortality of 16.4% in the pre-eICU period in 134 STEMI patients was reduced to 4.8% in 145 STEMI patients admitted during the eICU care model; a reduction of >70% in mortality (P<0.001). Of the 134 patients in the pre-eICU period, 68 patients received thrombolytic therapy with the mean door-to-needle time of 178.63 min, compared with 26.23 min in 145 patients in the post-eICU period (P<0.001). Mortality, even in the pre-eICU thrombolysed subgroup, was significantly higher as compared to the post-eICU period (13.2% vs. 4.8%, P<0.029). Moderate benefit. A study in Brazil in a tiered healthcare setting achieved in 22%, but only 5.4% survived to hospital discharge. |
| Saggu D    | Asia    | India   | 2014 | Catheter ablation in patients with electrical storm in early postinfarction period (6 weeks): A single center experience       | Retrospective (n=5). Patients with early VT storm following MI were treated with catheter ablation. 1 patient died from sepsis and 1 patient had recurrent VT. 3 patients remained VT-free. Predictors of neurologically favorable survival among patients with out-of-hospital cardiac arrest: A tertiary referral hospital experience. |
| Balci KG   | Eastern | Turkey  | 2017 | Predictors of neurologically favorable survival among patients with out-of-hospital cardiac arrest: A tertiary referral hospital experience. |

RCT: Randomized controlled trial, MI: Myocardial infarction, STEMI: ST segment elevation myocardial infarction, PCI: Percutaneous intervention, TIMI: Thrombolysis in myocardial infarction, IRA: Infarct-related artery, ACS: Acute coronary syndrome, CABG: Coronary artery bypass graft, AMI: Acute myocardial infarction, IABP: Inclined intra-aortic balloon bump, ECG: Electrocardiograph, VT: Ventricular tachycardia, ROSC: Spontaneous circulation, ACCES: Acute coronary events - a multinational survey of current management strategies, CSWT: Cardiac shock wave therapy.

not require laboratory capacity for cardiac enzymes but if used, troponin is the preferred biomarker for cardiac injury, and point of care testing can be used in rural settings.[10] Compared with high-income countries, the age distribution of patients presenting in ACS is younger, with 50% of patients from one case series in Pakistan younger than 55 years of age.[11] Men represent the majority of patients presenting with ACS across many sites.[12-16] Although men may have a higher incidence of ACS and coronary artery disease risk factors, men may also be more likely to present to care. A review of patients presenting to over 100 hospitals in India found no evidence of medical therapy and mortality between men and women.[17]

Early recognition seems to be key to providing a mortality benefit. A study in Brazil in a tiered healthcare setting found an average delay of 28 min from provider to EKG obtainment and another average 153 min for the percutaneous intervention (PCI) center to review the EKG and get the patient transferred.[18] In India, an electronic Intensive Care Unit (eICU) was established whereby EKGs were obtained and transmitted and interpreted by remote cardiologists, who made treatment recommendations resulting in the mean door to needle time of 30 min versus 180 min before eICU with a reduction of >70% in mortality.[19] Although IHD patients can be managed in a general medical ward, a specific cardiac unit may give evidence-based treatments more consistently and promptly.[20,21] In addition, units with cardiac monitors can detect arrhythmias or arrests more quickly with better outcomes.[22] On the contrary, thrombolytic use in the pre-hospital setting as well as improving PCI availability using tertiary center hospitals without access to cardiothoracic surgeons have both shown decreased mortality secondary to earlier diagnosis and intervention.[23,24]

Treatment

Evidence-based treatment of IHD can be applied in a stepwise manner, depending on the capacity of the facility and the financial resources of the patient and the payment model of the health care system. The first level of treatment is medical management. Medical management of ACS with propranolol was shown to improve the left ventricular ejection fraction (LVEF) and functional outcomes in India.[25]

The next level of treatment is systemic thrombolysis with streptokinase or tissue plasminogen activator (TPA); these medications can reduce mortality in LMIC.[24,26] Interventional approaches such as PCI with balloon angioplasty or stenting require greater infrastructure and more advanced practitioners. PCI was shown to have better outcomes than thrombolysis.[21] Compared with high-income countries, PCI tends to be used in
more acute situations rather than electively, but it can have comparable outcomes. Mortality is much higher in patients who present in cardiogenic shock, and time to patient presentation and outcomes vary by site.\textsuperscript{[15]} Using the transradial approach reduces hemorrhagic complications.\textsuperscript{[23]} When PCI does not successfully reopen the stenosed vessel, termed slow flow, patients have higher 30-day mortality.\textsuperscript{[28]} Abciximab administered intravenously has been used to treat slow flow states.\textsuperscript{[29]}

Finally, CABG can be used as an acute therapy for ACS. Even within a month, CABG improved LVEF following ACS.\textsuperscript{[30]} Despite the more invasive nature of CABG compared to PCI, CABG can have better outcomes and better cost-effectiveness than PCI in LMIC.\textsuperscript{[31]} Performing CABG off-pump reduces costs but has similar outcomes for low-risk patients with left main coronary artery disease.\textsuperscript{[32]} Some centers use CABG as the first-line therapy for critical left main stenosis and use PCI as a back-up for patients too critically ill to undergo surgery.\textsuperscript{[33]}

Patients in cardiogenic shock can be supported with inotropes, however, overall mortality is high, whether treated with PCI\textsuperscript{[12,34]} or CABG.\textsuperscript{[35]} Furthermore, for patients who present in cardiac arrest, survival to hospital discharge is around 5%.\textsuperscript{[36]}

The range of treatment options for ACS is not mutually exclusive. Thrombolysis can be administered during preparation for PCI,\textsuperscript{[34]} with similar outcomes with primary PCI and thrombolysis followed by PCI.\textsuperscript{[37]} In addition, PCI can treat occluded grafts that cause cardiac arrest following CABG.\textsuperscript{[38]} Furthermore, if the multi-vessel disease is diagnosed during PCI, CABG can be available as a further treatment option.\textsuperscript{[39]}

Other interventions that have been performed for patients with limited options included IABP for patients with refractory angina or cardiogenic shock.\textsuperscript{[40,41]} Cardiac shock wave therapy (CSWT) application to the ischemic myocardium in patients with refractory angina pectoris was found to improve symptoms and reduce the severity of ischemic areas at 6 months after CSWT treatment compared with the baseline.\textsuperscript{[42]}

**Stroke**

Within the stroke subgroup, articles were primarily from Asia (10), followed by Africa (5), Middle East (3), and Eastern Europe (2). Articles focused on diagnostic methods, body temperature, medications, thrombolysis, endovascular treatments, and system changes [Table 2].

**Diagnosis**

Clinical scoring systems to differentiate hemorrhagic versus ischemic stroke were found to be too unreliable to guide treatment decisions.\textsuperscript{[43]} Patients who present promptly with an ischemic stroke will have normal nonenhanced computed tomography (CT) scans. For those patients, CT perfusion (CTP), can be used to identify which patients have perfusion defects that might respond to thrombolysis, identifying two candidates out of 42 patients presenting with stroke.\textsuperscript{[44]} Accurately estimating stroke burden can be difficult, as a Ukrainian town prospective following of stroke patients found a burden above local statistics from death certificates but below WHO estimates. Thirty-day case fatality was 23.3%, including patients that died prior to reaching the hospital.\textsuperscript{[45]}

Hemorrhagic stroke can occur with acute hypertension and chronic hypertension is a risk factor. For patients who survive the initial bleed, complications include rebleeding and well as vasospasm. Vasospasm peaks in the 5–14 day period following the initial bleed.\textsuperscript{[46]}

**Thrombolysis**

A retrospective study of patients presenting to the emergency department with symptoms of acute stroke found that most present outside the window of treatment with thrombolysis. The nine patients who received TPA had similar mortality and functional outcomes as those who did not receive TPA, although the study was limited by small numbers and retrospective design.\textsuperscript{[47]} A retrospective look at two tertiary care centers in Pakistan found TPA used in 18/1185 (1.5%) stroke patient at one hospital and 3/575 (0.52%) patients at another hospital. Of the 21 patients who received the TPA, 7 (33%) were not eligible according to protocol, largely because of ischemic changes visible on head CT. Four of those patients had hemorrhage and three died.\textsuperscript{[48]} A review of 62 consecutive stroke patients presenting to a tertiary care hospital in India identified late presentations of patient, availability of CT, and the high cost of TPA as the major barriers to thrombolysis. Of the 62 patients, 7 presented within 3 h of stroke onset, had no contraindications to TPA, but did not receive TPA as the confirmatory CT did not happen until the patient was outside of the window.\textsuperscript{[49]}

**Endovascular interventions**

The use of endovascular techniques in subarachnoid hemorrhage resulted in 85% of patients without significant disability, and <2% had a procedure related fatality.\textsuperscript{[46]} Although no control group was used, this case series demonstrates good results from endovascular techniques. There were no primary studies found meeting the study criteria discussing endovascular techniques like thrombectomy in LMIC.

**Other interventions**

Patients with fever had mortality rates of 51.78% in those with hemorrhagic stroke and 56.66% in those with ischemic stroke, compared with 13.5% and 8.8% in normothermic groups, respectively.\textsuperscript{[50]} No data were
| Table 2: Stroke articles included |
|--------------------------------|
| **Author** | **Region** | **Country** | **Year** | **Title** | **Findings** |
| Dahn, et al.: Acute care for top 3 causes of death in LMIC |
| Gupta P | Asia | India | 2014 | Clinical predictors and outcome of patients of acute stroke requiring ventilatory support: A prospective hospital based cohort study | Prospective (n=193). Loss of consciousness at onset, progress of symptom and low motor GCS for ischemic stroke and low motor GCS and hematoma volume for hemorrhagic stroke are independent predictors of requirement of mechanical ventilation |
| Dochar DK | Asia | India | 2000 | Utilization and outcome of thrombolytic treatment for stroke | Prospective (n=240). The SSS and Allen Score, and their combination are not helpful in differentiating acute hemorrhagic from thrombotic CVA |
| Ekingen E | Africa | Nigeria | 2017 | Utilization of glial fibrillary acidic protein and galectin-3 in the diagnosis of cerebral infarction patients with normal cranial tomography | Prospective (n=90). Compared with healthy controls, biomarkers have 70.59% sensitivity and 70% specificity for ischemic stroke |
| Roy MK | Asia | India | 2003 | Effect of body temperature on mortality of acute stroke | Prospective (n=42). CTP may be a useful imaging tool for determining cerebral infarction in a rural-based community population, especially in cases where the unenhanced CT is normal. CTP was able to detect 22.7% of cerebral ischaemia with normal unenhanced CT in patients presenting <6 h after ictus. Thrombolysis is a therapeutic option, even when the history of onset of stroke is unclear. Ischemic stroke patients with normal unenhanced CT with no evidence to suggest infarction or hemorrhage should proceed to CTP in developing countries with these appropriate facilities |
| Man K | Asia | Malaysia | 2006 | Computed tomography perfusion of ischemic stroke patients in a rural Malaysian tertiary referral centre | Prospective (n=42). CTP may be a useful imaging tool for determining cerebral infarction in a rural-based community population, especially in cases where the unenhanced CT is normal. CTP was able to detect 22.7% of cerebral ischaemia with normal unenhanced CT in patients presenting <6 h after ictus. Thrombolysis is a therapeutic option, even when the history of onset of stroke is unclear. Ischemic stroke patients with normal unenhanced CT with no evidence to suggest infarction or hemorrhage should proceed to CTP in developing countries with these appropriate facilities |
| Body temp | Roy MK | Asia | India | 2004 | Effect of body temperature on mortality of acute stroke | Prospective (n=200). Hyperthermia was associated with higher mortality rate in hemorrhagic and ischemic stroke cases. Hypothermia (<36.5 degrees) was associated with 0% mortality |
| Medications | Gupta RC | Asia | India | 1978 | Betamethasone therapy in acute cerebrovascular accidents | Prospective RCT (n=49). No mortality benefit to high-dose steroids in patients with acute CVA |
| Dalal PM | Asia | India | 1995 | Use of calcium channel blockers in acute ischemic cerebrovascular disease | Prospective (n=80). Administration of Nimodipine in patients with acute ischemic CVA showed significant improvement in quality of neurologic recovery but no change in mortality |
| Ogun SA | Africa | Nigeria | 2001 | Effectiveness of high dose dexamethasone in the treatment of acute stroke: a preferred antihypertensive therapy for acute intracerebral hemorrhage? | Prospective RCT (n=230). No mortality benefit to a short course of high-dose steroids in patients with acute CVA |
| Kalita J | Asia | India | 2013 | Is beta-blocker (atenolol) a preferred antihypertensive in acute intracerebral hemorrhage? | Prospective (n=138) patients with hypertensive ICH, Atenolol significantly reduced the mortality (11.4 vs. 37.3%, P<0.0001), SIRS (16.4 vs. 40.9%, P=0.007), and pneumonia (8.9 vs. 30.5%, P=0.002) compared to those not receiving atenolol |
| Wasay M | Middle East | Pakistan | 2008 | A non-randomized study of safety and efficacy of heparin for DVT prophylaxis in intracerebral hemorrhage | Retrospective (n=458). Subcutaneous heparin in doses of 2500-5000 units twice daily during acute phase in patients with ICH may be safe for DVT prophylaxis |
| Thrombolytics | Nandigam K | Asia | India | 2003 | Feasibility of acute thrombolytic therapy for stroke | Retrospective (n=64). This study identifies many hurdles in delivering thrombolytic therapy to eligible patients with acute ischemic stroke in rural India. Lack of public awareness, poor health-care delivery systems, and nonaffordability of treatment costs were the main factors |
| Wasay M | Middle East | Pakistan | 2010 | Utilization and outcome of thrombolytic therapy for acute stroke in Pakistan | Retrospective (n=21). TPA was associated with high morbidity (24% ICH) and mortality (19%) due to protocol violations (error interpreting CT scan and delay in administration time) |
| El Sayed MJ | Middle East | Lebanon | 2014 | Acute stroke care and thrombolytic therapy use in a tertiary care center in Lebanon | Retrospective (n=67). TPA does not make a difference in ischemic CVA |
| Abraham SV | Asia | India | 2017 | The need for a population-based, dose optimization study for recombinant tissue plasminogen activator in acute ischemic stroke: A study from a tertiary care teaching hospital from South India | Prospective (n=159). When comparing weight-based dosing of TPA, patients with 0.7-0.8 mg/kg rather than the internationally recommended 0.9 mg/kg had better outcomes. Due to the small study size, results were not statistically significant |
| Endo-vascular | Scheglov DV | Eastern Europe | Ukraine | 2015 | Endovascular treatment of vasospasm related to acute subarachnoid hemorrhage from ruptured aneurysms | Retrospective (n=174). Patients with ruptured SAH Tx with endovascular techniques; Endovascular methodology allows aneurysm occlusion and treatment of vasospasm (a main complication of acute aneurysmal hemorrhage) and thus can significantly improve outcomes |

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presented on whether therapeutic interventions to reduce hyperthermia affect mortality. Controlling blood pressure after a hemorrhagic stroke prevents extension of the bleed. A nonrandomized trial of atenolol versus other antihypertensives found 11.4% mortality in the atenolol group compared with 37.3% in the nonatenolol group.\(^5\) In 1995, Dalal and Dalal found that nimodipine started early after diagnosis of an ischemic stroke resulted in reduced disability, although no impact on mortality: 77.6% compared with 58.1% in the control group showed improved functional status.\(^6\) Introducing a dedicated stroke ward reduced mortality from 8.9% to 2.1%, with an associated decrease in pneumonia, hemorrhage, and pressure sores while also reducing the average length of stay.\(^7\) Presence of factors such as low Glasgow Coma Scale (GCS) or clinical progression is associated with the need for mechanical ventilation.\(^8\) A nonrandom comparison of heparin plus elastic stockings compared with elastic stockings alone for deep vein thrombosis (DVT) prevention found only one DVT in the stocking group. A total of 12% of patients in the heparin group died compared with 20% in the control group, suggesting that heparin is safe for DVT prophylaxis in patients with acute intracerebral hemorrhage.\(^9\)

In 1978, Gupta et al. randomized patient to steroids or placebo and found improved survival in patients with hemorrhage receiving steroids, but overall, no significant difference was found with steroids.\(^10\) Over two decades later in 2001, Ogun used much higher doses of steroid and had higher overall mortality, but found no difference in mortality compared with placebo.\(^11\) Other treatments under investigation include transcranial magnetic stimulation to improve motor function following stroke.\(^12\)

### Lower respiratory infection

Within the LRI adult subgroup, articles were primarily from Asia (9) and Eastern Europe (6), followed by Africa (5), the Middle East (4), and multiple regions (3) [Table 3]. Within the LRI pediatric subgroup, articles were primarily from Asia (30), followed by Africa (22) and the Middle East (7), Eastern Europe (4), and multiple regions (8), with very few from Oceania (2), South America (2), and Central America (1) [Table 4].

#### Level of care

Acute LRIs present with a range of severity in part depending on comorbidities. Various severity scores and risk factors are associated with mortality including CURB65 and CRB65 as well as Acute Physiology and Chronic Health Evaluation II (APACHE II).\(^13\) A low-risk subsection of patients can be treated at home, whereas others require hospitalization and even intensive care. Patients treated in intensive care or admitted with severe pneumonia have mortality ranging from 20% to 50% depending on the report.\(^14\) The strategies to reduce mortality include respiratory support, antibiotics, and adjuvant therapies.

#### Noninvasive ventilation

Patients with acute lower respiratory tract infection
Table 3: Lower respiratory infections adult articles included

| Author     | Region | Country     | Year | Title                                                                 | Findings                                                                                                                                 |
|------------|--------|-------------|------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Calligaro GL | Africa | South Africa | 2015 | Burden of tuberculosis in ICU in Cape Town, South Africa, and assessment of the accuracy and effect on patient outcomes of the Xpert MTB/RIF test on tracheal aspirate samples for diagnosis of pulmonary tuberculosis: A prospective burden of disease study with a nested randomized controlled trial | Prospective RCT (n=341). Intubated patients suspected of having tuberculosis were tested with tracheal aspirates with GeneXpert with 15% found to be positive. GeneXpert was more sensitive than culture |
| Chinchkar NJ | Asia   | India       | 2015 | A stepwise approach to the etiologic diagnosis of pleural effusion in respiratory ICU and short-term evaluation of treatment | Prospective (n=50). Effusion accompanying pneumonia compared with pneumonia alone increases the mortality risk by 3.4 times in unilateral and 7 times in bilateral effusions. In this series, in-hospital mortality in para-pneumonic effusion was 37% against an overall mortality of 20%. It is imperative to establish the diagnosis before starting the treatment |
| Adebonojo SA | Africa | Nigeria     | 1979 | Lung abscess: A review of 3-years’ experience at the University College Hospital, Ibadan | Retrospective (n=45). 45 patients with lung abscesses were treated over 3 years. 29 were treated medically and 5 died. 16 were treated surgically and six died. CXR showed air fluid levels. Sputum culture grew out a single organism is 11. Massive hemoptysis was the primary indication for surgical intervention |
| Scott JAG  | Africa | Kenya       | 2000 | Etiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya | Prospective (n=281). Patients with pneumonia had blood cultures, lung aspiration and serology to assess for etiology. 65% of patients had an etiology identified. S. pneumonia was the most common pathogen, but 9% were diagnosed with tuberculosis. The data supports empiric treatment for S. pneumonia, but patients should also be tested for tuberculosis |
| Zuberi FF  | Middle East | Pakistan | 2008 | Prospective comparison of prediction rules of mortality risk for CAP in a developing country | Prospective (n=137). Patients with pneumonia were assessed with CURB65 and CRB65, which both had good ROC for mortality and identified a low-risk subsection that could be treated at home |
| Belle J    | Africa | -           | 2010 | Influenza preparedness in low-resource settings: A look at oxygen delivery in 12 African countries | Survey (n=231 sites). Facilities in 12 African countries were surveyed and 43.8% reported always having access to a source of oxygen, whether cylinder or concentrator. Oxygen concentrators require a dependable electricity supply but are cheaper than oxygen cylinders and do not require replacement. Oxygen is listed as essential medicine by WHO but is not readily available in many places |
| Narimanian M | Eastern Europe | Armenia | 2005 | Impact of Chisans (ADAPT-232) on the quality-of-life and its efficacy as an adjuvant in the treatment of acute nonspecific pneumonia | Prospective RCT (n=60). ADAPT-232 a mix of plant extracts, speeds the recovery from pneumonia and increases the quality of life during convalescence in a placebo controlled trial |
| Brown N    | Multiple | -           | 2004 | Vitamin A for acute respiratory infection in developing countries: A meta-analysis | Systematic Review (n=5 studies). A meta-analysis of five studies of Vitamin A in acute lower respiratory tract infections showed no difference in recovery or mortality |
| Rubach MP  | Africa | Tanzania    | 2015 | Etiologies of illness among patients meeting integrated management of adolescent and adult illness district clinician manual criteria for severe infections in northern Tanzania: Implications for empiric antimicrobial therapy | Retrospective (n=423). Illness etiologies: septic shock, severe respiratory distress with/without shock, PNA. Ceftriaxone had the highest utility. Other diseases (cryptococcosis, histoplasmosis, q fever, Ricketsial diseases) were common and need specific treatment |
| Khan S     | Asia   | Pakistan    | 2003 | Cefaclor AF versus clarithromycin in acute exacerbation of chronic bronchitis | Prospective (n=300). Patients with COPD exacerbation were treated with cefaclor or clarithromycin with similar efficacy. COPD exacerbations are not always bacterial, but antibiotics can produce clinical improvement |
| Hui DS     | Asia   | Indonesia, Philippines, Korea, Thailand, Malaysia, Taiwan | 2011 | A multicenter surveillance study on the characteristics, bacterial etiologies and in vitro antibiotic susceptibilities in patients with acute exacerbations of chronic bronchitis | Prospective (n=447). Sputum cultures of patients with acute COPD exacerbations showed a range of pathogens depending on countries, including Pseudomonas in some countries. Overall, fluoroquinolones showed high susceptibilities and are a good empiric choice |
Table 3: Contd...

| Author         | Region     | Country       | Year | Title                                                                 | Findings                                                                                                                                                                                                 |
|----------------|------------|---------------|------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dahn, et al.   | Asia       | India         | 1991 | Albendazole in the treatment of pulmonary echinococcosis             | Retrospective (n = 10). Albendazole has been used with success in hydatid cyst of the liver. 10 children with hydatid cyst of the lung were treated with albendazole without any improvement                                       |
| Qazi SA        | Asia       | Pakistan      | 1999 | Antibiotic strategies for developing countries: Experience with acute respiratory tract infections in Pakistan | Review (n = 6 studies). A series of studies in Pakistan evaluating the WHO recommended course of co-trimoxazole found rising failure rates, although the success rates were much higher than would be suggested by the high in vitro rates of S. pneumonia and H. influenzae to co-trimoxazole. In vitro data does not correlate to clinical outcomes |
| Rammaert B     | Asia       | Cambodia      | 2013 | Acute LRI on lung sequela in Cambodia, a neglected disease in highly tuberculosis-endemic country | Prospective (n = 1800). Cambodia has high rates of both tuberculosis and other infectious lung pathologies. A review of adult lower respiratory infection patients revealed that many had scarring, retraction, or cavitations suggestive of prior lung infection, particularly as patients got older. Many of these patients were inaccurately treated for active tuberculosis or were given antibiotics which would not cover the colonizing bacteria |
| Mehrgan H      | Middle East| Iran          | 2010 | High prevalence of ESBL producing K. pneumoniae in a tertiary care hospital in Tehran, Iran | Prospective (n = 202). Of isolates of Klebsiella pneumonia, 77.7% produce ESBL. While the study included majority of urinary specimens, the findings held true for respiratory specimens. Based on individual sensitivity testing, the most widely efficacious antibiotic was Imipenem |
| Khawaja A      | Middle East| Pakistan      | 2013 | Etiology and outcome of severe community acquired pneumonia in immunocompetent adults | Retrospective (n = 189). Of patients admitted with severe community acquired pneumonia, overall mortality was 51%. Mortality was even higher in patients with septic shock, and with pseudomonas or S. aureus. Despite blood cultures on every patient and many patients having BAL cultures, only 25% of patients had a specific infectious pathogen identified. Given this low yield and the delayed results of cultures, treatment has to be started empirically and should reflect the local epidemiology |
| Moghnieh R     | Middle East| Lebanon       | 2014 | The LSIDCM Guidelines for Adult CAP                                  | Review. Compared to Saudi/GCC guidelines, in Lebanon they suggest adding a B-lactam antibiotic + macrolide for monotherapy in outpatients with no comorbidities due to macrolide resistance. CXR is routine for diagnosis. Antivirals empiric is not recommended for suspected viral PNA. For ICU patients, give nonantipseudomonal 3rd gen cephalosporin + azithromycin or clarithromycin or b-lactam + respiratory fluoroquinolone for low-pseudomonal risk. If high pseudomonal risk, give anti-pneumococcoal and anti-pseudomonal b-lactam (pipercillin/tazobactam) or cefepime or meropenm or imipen + either ciprofloxacin or levofloxacin |
| Sow O          | Multiple   | Guinea and France | 1996 | Community acquired pneumonia in adults: A study comparing clinical features and outcome in Africa (Republic of Guinea) and Europe (France) | Prospective (n = 333). A cohort of patients with CAP in France were significantly older with more comorbidities than in Conakry, while those in Conakry were more likely to have initial shock and herpes. Mortality (6% vs. 8%) and clinical recovery (88% vs. 85%) were similar in both settings despite penicillin along being used in the majority of cases in Conakry and multiple or second line antibiotics being often used in France |
| Treatment:     |            |              |      |                                                                      |                                                                                                                                                                                                     |
| Karakurt Z     | Eastern    | Turkey        | 2010 | Influenza A (H1N1) virus pneumonia in ICU                           | Retrospective (n = 19). Patients admitted to the ICU with suspected H1N1 influenza. 4/19 died. NIMV was used successfully in many of the patients                                                                 |
| Agarwal R      | Asia       | India         | 2009 | Outcomes of NIV in acute hypoxic respiratory failure in a respiratory ICU in North India | Prospective (n = 287). 138 patients were admitted to the ICU with acute hypoxic respiratory failure. 98 required immediate intubation. 40 were trialed on noninvasive ventilation, and 47.6% of those patients subsequently required intubation. For a group largely composed of ARDS patients, NIV had a high failure rate. The worse the blood gas initially, the higher the risk of subsequent intubation. The authors conclude that although NIV had good outcomes with COPD and cardiogenic pulmonary edema, patients have to be carefully selected if they have other etiology of respiratory failure |
may require some degree of respiratory support, in a continuum from supplemental oxygen, to noninvasive mechanical ventilation, to intubation. Each of these supports can be offered even if more advanced supports are not available as backup.

Oxygen is listed as an essential medicine by the WHO[63] but is not readily available in many places. A total of 231 facilities in 12 African countries were surveyed, and 43.8% reported always having access to a source of oxygen, whether cylinder or concentrator. Oxygen concentrators require a dependable electricity supply but are cheaper than oxygen cylinders and do not require replacement.[64]

The Philippines established a national program for control of acute respiratory infection, and with donor support were able to roll out training and medications and supplies such as oxygen throughout the country. Without on-going donor support, however, the supply lines were unable to be maintained, and the measurement

### Table 3: Contd...

| Author        | Region    | Country     | Year | Title                                                                 | Findings                                                                                     |
|---------------|-----------|-------------|------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Borse RT      | Asia      | India       | 2013 | Comparison of demographic, clinical, radiological characteristics and comorbidities in mechanically ventilated and nonventilated, adult patients admitted in ICU with confirmed diagnosis of influenza A (H1N1) | Retrospective (n=100). Increased mechanical ventilation requirement in: Female with pregnancy, DM, HTN, tachyphoea, bilateral lung involvement or involvement of RU/middle/multiple zones. Also, cardiac involvement, RU/RM/LM/LR lung fields, cardiomegaly |
| Teke T        | Eastern   | Turkey      | 2011 | 2009 H1N1 Influenza and Experience in Three Critical Care Units    | Retrospective (n=61). Patients were admitted to ICU in Turkey with H1N1. Mortality 50.8% overall. Many patients had hypoxemic respiratory failure. Use of NIV was associated with increased survival. Higher APACHE II score was associated with increased mortality |
| Cilli A       | Eastern   | Turkey      | 2013 | CAP in patients with COPD requiring admission to the ICU: Risk factors for mortality | For patients with COPD with CAP treated in the ICU, mortality is high (23.9%). NIPPV and corticosteroids reduced mortality, and bilateral infiltrates were associated with higher mortality. CAP was diagnosed with new infiltrate on CXR. The use of NIV has been questioned in the treatment of CAP for patients without COPD, but serves as a standard treatment for COPD exacerbations |
| Erdem H       | Eastern   | Turkey      | 2013 | Mortality indicators in CAP requiring intensive care in Turkey     | Prospective (n=211). Patients with CAP requiring ICU admission across multiple hospitals were reviewed for risk factors for mortality. Bilateral involvement and increased severity score were associated with mortality. Baseline hypertension and use of noninvasive ventilation were protective against mortality. Overall mortality was 31%. A large portion of patients in the study had COPD, which might explain the benefit observed with NIV. Almost 20% of patients did not have any culture or other microbiology tests to guide treatment |
| Ciledag A     | Eastern   | Turkey      | 2014 | The risk factors for late failure of noninvasive mechanical ventilation in acute hypercapnic respiratory failure | Prospective (n=93). Risk factors: High APACHE II score, high CRP level, low GCS, low albumin, weak cough, bad compliance to noninvasive mechanical ventilation, the presence of bronchiectasis/PNA, absence of determined risk factors |
| Martin S      | Multiple  | -           | 2014 | Efficacy and safety of bubble CPAP in neonatal care in low- and middle-income countries: A systematic review | Systematic review (n=14). Evidence that bubble CPAP is safe and reduces need for mechanical ventilation for infants < 28 days, but more research/efficacy is needed because meta-analysis failed to show a significant improvement |
| System        | Hadi A    | Bangladesh  | 2003 | Management of acute respiratory infections by community health volunteers: Experience of BRAC | Retrospective (n=3567). Community health volunteers trained to diagnosed and manage acute respiratory infections were observed by physicians. Volunteers who had received basic training and had regular supervision performed better. Regularly supervised volunteers diagnosed and treated over 90% of children correctly. Sometime, miscategorizing between severe and very severe would not change management as both categories would be referred for further assessment |

MTB/RIF: Mycobacterium tuberculosis / rifampicin resistance, NIV: Non-invasive mechanical ventilation, CXR: Chest X-ray, CAP: Community-Acquired Pneumonia, WHO: World Health Organization, ROC: Receiver operating characteristic, RCT: Randomized controlled trials, COPD: Chronic obstructive pulmonary disease, ESBL: Extended-spectrum beta-lactamase, PNA: Pneumonia, BAL: Bronchial alveolar lavage, GCC: Gulf Cooperation Council, LSIDCM: Lebanese Society for Infectious Diseases and Clinical Microbiology, NIV: Noninvasive ventilation, ARDS: Acute respiratory distress syndrome, DM: Diabetes mellitus, ICU: Intensive Care Unit, HTN: Hypertension, BRAC: Bangladesh Rural Advancement Committee, S. pneumoniae: Streptococcus pneumoniae, K. pneumoniae: Klebsiella pneumoniae, S. aureus: Staphylococcus aureus, LRI: Lower respiratory infections, CPAP: Continuous positive airway pressure, H. influenzae: Haemophilus influenzae, AF: Advanced formulation, NIPPV: Noninvasive positive pressure ventilation
Table 4: Lower respiratory infections pediatric articles included

| Author       | Region       | Country            | Year | Title                                                                 | Findings |
|--------------|--------------|--------------------|------|----------------------------------------------------------------------|----------|
| Dahn, et al. | Asia         | India              | 2009 | Acute care for top 3 causes of death in LMIC                          |          |
| Onyango FE   | Africa       | Kenya              | 1993 | Hypoxemia in young Kenyan children with ALRI                         | Prospective (n=256). Children <3 with acute ALRI were assessed for hypoxemia. Oxygen saturation <90% was associated with 4.3 fold increase in short term mortality. Clinical correlates of hypoxemia included elevated respiratory rate, grunting, and retractions. Hypoxemia also predicted radiographic pneumonia, but radiographic pneumonia was not associated with death |
| Madico G     | South America| Peru               | 1995 | The role of pulse oximetry. Its use as an indicator of severe respiratory disease in Peruvian children living at sea level. Respiratory group in Peru | Prospective (n=269). Pulse oximetry is just as sensitive and more specific than the WHO algorithm in identifying children with ALRI. The WHO algorithm identified 35% of well children as having respiratory infection compared with 4% by pulse oximetry |
| Pepin J      | Africa       | Central African Republic | 2001 | ALRIs among children hospitalized in Bangui, Central African Republic: toward a new case-management algorithm | Prospective (n=505). The IMCI defines pneumonia based on tachypnea and severe pneumonia based on chest indrawing. In a year of children presenting to a hospital in CAR, mortality for children with pneumonia was 1/130, but 43/238 (18.1%) for those with severe pneumonia. Desaturation, nasal flaring, and grunting were also associated with greater mortality. Chest indrawing had equal mortality, whether or not associated with tachypnea |
| Laman M      | Oceania      | Papua New Guinea   | 2005 | Can clinical signs predict hypoxemia in Papua New Guinean children with moderate and severe pneumonia? | Prospective (n=200). Children were admitted with severe pneumonia. Over half needed change of antibiotics due to worsening clinical status, and 10.5% died. Lack of exclusive breast feeding and low birth weight was associated with antibiotic failure, and pallor was associated with mortality |
| Tiewsoh K    | Asia         | India              | 2009 | Factors determining the outcome of children hospitalized with severe pneumonia | Prospective (n=77). Children with ALRI were evaluated. Cyanosis and head nodding had good specificity for hypoxemia but not sensitivity. Pulse oximetry cannot be replaced with clinical observations |
| Rao YK       | Asia         | India              | 2012 | Clinical predictors of hypoxemia in Indian children with acute respiratory tract infection presenting to pediatric emergency department | Cross-sectional (n=261). Chest retractions were the most sensitive measure of hypoxemia in children and cyanosis was the most specific, but no measure had both good sensitivity and good specificity. Clinical exam cannot reliably replace pulse oximetry |
| Modi P       | Africa       | Rwanda             | 2013 | Oxygen saturation can predict pediatric pneumonia in a resource-limited setting | Retrospective (n=147). Oxygen saturation predicts radiographically diagnosed pneumonia in children. Respiratory rate did not predict pneumonia. Children without history of asthma, and those with negative malaria blood smear were more likely to have pneumonia |
| Mahajan V    | Asia         | India              | 2016 | Clinical predictors of hospital admission in acute LRTI in 2 months to 2-year-old children | Prospective (n=240). Children, of whom 130 were admitted, had a multivariable analysis which showed that tachypnea, retractions, fever, hypoxia and reduced GSC were associated with admission. Lower GCS and hypoxia had the strongest relationship with admission |
| Pedraza-Bernal | South America | Colombia          | 2016 | Predictors of severe disease in a hospitalized population of children with acute viral LRTIs | Prospective (1180). Of 416 children admitted with ARI who were positive for virus, admission to PICU was associated with underlying pulmonary hypertension or recurrent wheeze. The specific viral was not associated with increased severity |
| Siguque B    | Africa       | Mozambique         | 2009 | Severe pneumonia in Mozambican young children: Clinical and radiological characteristics and risk factors | Prospective (n=757). Children admitted with severe pneumonia all had CXR, malaria and HIV testing. If pneumonia is clinically diagnosed based on cough and rapid breathing, children with malaria can be misdiagnosed as having pneumonia. In this study, a positive malaria parasitemia was less likely to have radiographically pneumonia. HIV infection was associated with higher mortality. Clinical case definitions may be misleading in places with HIV and malaria |

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Table 4: Contd...

| Author           | Region | Country   | Year | Title                                                                 | Findings                                                                                                                                 |
|------------------|--------|-----------|------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Seear M          | Asia   | India     | 2016 | Predictive accuracy of chest radiographs in diagnosing tachypneic children | Prospective (n=134). Children with tachypnea had CXR. Except for pleural effusions, the CXR had poor inter-observer agreement, and poor correlation with clinical diagnosis |
| Usen S           | Africa | Gambia    | 1999 | Clinical predictors of hypoxemia in Gambian children with acute LRTI: Prospective cohort study | Prospective (n=1072). Children admitted to the hospital with acute LRTI were evaluated for clinical predictors of hypoxemia, which was found in 63 children. The children with hypoxemia had five times the mortality rate of children without hypoxemia. Cyanosis, rapid respiratory rate, and head nodding were associated with hypoxemia and rapid respiratory rate had sensitivity of 70% and specificity of 79% |
| Aiyieko P        | Multiple | -      | 2007 | Case management of childhood pneumonia in developing countries       | Review. Articles evaluating portions of WHO case management. The diagnostic criteria of tachypnea had high sensitivity but low specificity and chest indrawing had variable sensitivity. The definitions of severe and very severe pneumonia are associated with worse outcomes. Chloramphenicol for severe pneumonia shows treatment success >80%. Studies showed variable definitions of treatment failure |
| Diagnosis:      | Chavez MA | Multiple | Peru, Nepal | Agreement Between ultrasound and Lung Consolidation Identified Using POCUS for the Diagnosis of Childhood Pneumonia by General Practitioners | Prospective (n=376). The WHO algorithm disagreed with POCUS findings in more than 1/3 of children and had an overall low performance when compared with POCUS to identify lung consolidation |
| CXR              | Nagoran K | Africa | Cote d'Ivoire | Acute pneumonia in infants in Côte d'Ivoire: contribution of chest radiography in etiological research and early management | Retrospective case series (n=165). Chest radiography in children under 24 months not only helped establish the diagnosis of pneumonia, but helped narrow down the type of pneumonia, guiding therapy |
| Fancourt N       | Multiple | Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, Zambia | 2017 | Chest radiograph findings in childhood pneumonia cases From the MultiSite PERCH Study | Prospective (n=4232). For children meeting the clinical definition of pneumonia, only 54% had abnormal CXR, either consolidation or infiltrate. Consolidation was associated with CFR of 13.5% compared with 5% for either normal or infiltrate. CXR has high specificity but low sensitivity for pneumonia but is associated with higher mortality |
| Diagnosis:      | Onipede AO | Africa | Nigeria | Invasive bacteria isolates from children with severe infections in a Nigerian hospital | Prospective (n=90). Of patients with pneumonia, 18 had pathogen identified with blood cultures, of which 15 were S. aureus. Susceptibility was higher to fluoroquinolones than other agents. The study showed higher yields for patients with sepsis or meningitis as primary diagnosis |
| Saha S           | Asia   | Bangladesh | 2009 | Surveillance for invasive Streptococcus pneumoniae disease among hospitalized children in Bangladesh: Antimicrobial susceptibility and serotype distribution | Prospective (n=13). Blood and CSF cultures were taken from children to detect S. pneumonia and sensitivity and serotype. Only 0.3% of children with pneumonia had S. pneumonia in their blood. The serotypes can guide decisions regarding vaccine interventions. High frequencies of resistance to cotrimoxazole were found |
| Elkholy A        | Middle East | Egypt | 2009 | Acute LRTI due to Chlamydia and Mycoplasma spp. in Egyptian children under 5 years of age | Prospective (n=111). Children with acute LRTI had serological testing for chlamydia and mycoplasma, which were at 11.7% and 4.5%, respectively. Clinical characteristics could not differentiate between those with these atypical organisms and nonpathogens |
| Schwarz NG       | Africa | Ghana     | 2010 | Systemic bacteremia in children presenting with clinical pneumonia and the impact of NTS | Prospective (n=173). Children with clinical symptoms of pneumonia had blood cultures done. Blood cultures in about 20% were positive, and the most common pathogen (16/40) was nontyphoidal Salmonella. The nontyphoid Salmonella had high rates of resistance to antibiotics other than ceftriaxone and ciprofloxacin. In conclusion, patients with sepsis can present in respiratory distress and antibiotics such as amoxicillin are not adequate coverage for empiric treatment for children with presumed pneumonia |

Contd...
| Author | Region | Country | Year | Title | Findings |
|--------|--------|---------|------|-------|----------|
| Hadi N | Middle East | Iran | 2011 | Survey of M. Pneumoniae in Iranian children with ALRIs | Prospective (n = 100). *M. pneumoniae* was isolated with PCR from throat swabs of 10% of children treated both inpatient and outpatient for LRTI. Clinical and laboratory characteristics did not differentiate between patients with *M. pneumoniae* and other etiologies. PCR could be used to diagnose *M. pneumoniae*, or antibiotics should be tailored to cover atypical organisms. |
| Chisti MJ | Asia | Bangladesh | 2014 | A Prospective Study of the Prevalence of TB and Bacteremia in Bangladeshi Children with Severe Malnutrition and Pneumonia Including an Evaluation of Xpert MTB/RIF Assay | Prospective (n = 405). Kids <5 years old: TB is common (21%) in malnourished children with PNA. X-part MTB/RIF assay has better case detection rate compared to sputum microscopy and culture. |
| Keitel K | Africa | Tanzania | 2017 | A novel electronic algorithm using host biomarker point-of-care tests for the management of febrile illness in Tanzanian children (e-POCT): A randomized, controlled noninferiority trial | Case-control (n = 432). Comparing yield of PCR of NP/OP with induced sputum found little difference in yield of viral or bacterial etiology in children with pneumonia, except in the case of pertussis. IS in children is likely not worth the added cost for either surveys or direct patient care. |
| Thea DM | Multiple | Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, Zambia | 2017 | Limited utility of PCR in induced sputum specimens for determining the causes of childhood pneumonia in resource-poor settings: Findings from the PERCH Study | Limited utility of PCR in induced sputum specimens for determining the causes of childhood pneumonia in resource-poor settings: Findings from the PERCH Study. |
| System Khan AJ | Middle East | Pakistan | 1990 | ARIs in children: a case management intervention in of Abbottabad District, Pakistan | Intervention (n = 17). CHWs were trained in ARI case management. They lived in intervention villages and visited households in active case finding. They would administer antibiotics if appropriate and also give maternal education of home care and warning signs. ALRI specific child mortality was 6.3 per 1000 in the intervention villages and 14.4 in the control villages, where the mortality fell to 6.5 once the intervention was rolled out. Total child mortality fell by 29% following the intervention. |
| Fagbule D | Africa | Nigeria | 1994 | ARIs in Nigerian children: Prospective cohort study of incidence and case management | Surveillance (n = 481). CHWs made thrice weekly visits to the homes of 481 children over the course of a year. There were 13 episodes of pneumonia per child per year with three total ARI infections per child per year. The CHWs did an accurate job of diagnosis and management. Mild ARI were treated at home, but 19% were recommended antibiotics. The severe cases were all referred to hospital, and of the moderate cases treated at home, 71% achieving appropriate treatment. No child died from ARI during the study period. Trained CHW can accurately triage children, referring those who need to the hospital. |
| Habib OS | Middle East | Iraq | 1994 | ARIs: A study on case management in Basrah health centers | Observation (n = 392). Children observed receiving treatment in 12 health centers showed that 55.3% of mild ARI received antibiotics. Moderate cases were appropriately treated with antibiotics at home. Severe cases received antibiotics, but only 68.4% were appropriately referred to hospital. Only 5% of the cases were severe. |
| Tawfik Y | Africa | Uganda | 2006 | Negotiating improved case management of childhood illness with formal and informal private practitioners in Uganda | Intervention (n = 20). Private practitioners had simulated interview on caring for children, then training, then repeat simulated patient encounter. From baseline to post, practitioners increased from 0 to 85% giving the correct medicine for pneumonia. The percent warning on danger signs needing immediate care increased from 2 to 41%. |

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Table 4: Contd...

| Author          | Region  | Country   | Year | Title                                                                 | Findings                                                                                                                                                                                                 |
|-----------------|---------|-----------|------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dahn, et al.    |         |           |      | Acute care for top 3 causes of death in LMIC                          |                                                                                                                                                                                                          |
| Bharti B        | Asia    | India     | 2007 | Role of AIOS in managing severe childhood pneumonia                   | Prospective ($n = 89$). The Acute Illness Observational Scale in which clinicians score patients based on hydration, color, interactiveness and other qualities correlates with which children with severe pneumonia needed parenteral antibiotics or IV hydration and could be used to guide which children are hospitalized versus treated at home |
| Quiambao BP     | Asia    | Philippines | 2007 | Serious community-acquired neonatal infections in rural Southeast Asia (Bohol Island, Philippines) | Retrospective ($n = 264$). Infants <2 months of age presented with pneumonia to a rural hospital in the Philippines. The younger the child, the higher the risk of death. Radiographic pneumonia was also associated with higher rate of death. For children who had blood culture that grew an organism that was resistant to the initial choice of antibiotic, the chance of death was higher. Empiric ampicillin and gentamicin would cover most of the isolates in the study |
| Webb C          | Africa  | Kenya     | 2012 | Treatment Failure Among Kenyan Children With Severe Pneumonia—A Cohort Study | Prospective ($n = 2035$). Children with severe pneumonia were treated according to the WHO protocol, and assessed for treatment failure at 48 h, 5 days, and mortality. Mortality was highest in children with very severe pneumonia, defined as central cyanosis, inability to drink, or reduced level of consciousness. Mortality was very low (1/403) in children without very severe pneumonia, even in children with HIV or severe malnutrition, although these children had an increased risk of treatment failure at 48 h. Children tended to die within 48 h based on severity of clinical status at presentation, suggesting a need for prevention or education to encourage earlier presentation. Pulse oximetry predicted outcomes |
| Chisti MJ       | Asia    | Bangladesh | 2013 | Clinical Risk Factors of Death From Pneumonia in Children with SAM in an Urban Critical Care Ward of Bangladesh | Retrospective ($n = 50$). Children with SAM have higher mortality from community acquired pneumonia. A retrospective case controlled study looked at the factors associated with mortality in this population. Volume depletion and hypoxia which was treated with nasal cannula or non-rebreath was associated with mortality, and blood transfusion for fluid resistant hypotension were associated with mortality. Blood transfusions should not be given for fluid-resistant hypotension. The authors conclude that prompt parenteral antibiotics should be administered to children with hypoxia, volume depletion, and abdominal distension |
| Sutcliffe CG     | Africa  | Zambia     | 2016 | A clinical guidance tool to improve the care of children hospitalized with severe pneumonia in Lusaka, Zambia | Prospective ($n = 693$). 250 children admitted with severe pneumonia were treated after introduction of a clinical guidance tool. The tool did not change overall mortality at 18.2%, but increased the percentage of hypoxic children placed on supplemental oxygen and increased the proportion of children with HIV who received bactrim |
| English M       | Africa  | Kenya      | 1996 | Clinical overlap between malaria and severe pneumonia in African children in hospital | Prospective ($n = 175$). Children admitted to the hospital with respiratory symptoms and who received a CXR were included in the study. 26 had a consolidation on CXR and negative smear for malaria. 69 had high parasitemia and negative CXR. Comparing these two groups, the children with malaria had higher oxygen saturation, lower hemoglobin, but higher lactate and urea. The rest of the children had signs of overlapping clinical syndromes, such as positive blood smear and consolidation. While malaria alone can give respiratory symptoms that can be misattributed to pneumonia, pneumonia and malaria can co-occur in endemic symptoms and treatment for both should be considered |
| Singhi SC       | Asia    | India      | 2012 | Potential risk of hypoxemia in patients with severe pneumonia but no hypoxemia on initial assessment: a prospective pilot trial | Prospective ($n = 58$). Children with severe pneumonia but oxygen saturation >90% were monitored and 53% subsequently developed hypoxia. Prophylactic oxygen administration did not alter outcomes |
| Author                | Region    | Country | Year  | Title                                                                 | Findings                                                                                                                                 |
|----------------------|-----------|---------|-------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment: Oxygen    | Weber MW  | Africa  | 1996  | Humidification of oxygen with unheated humidifiers in tropical climates | Prospective (n = 123). Unheated humidifiers for oxygen resulted in low temperature of the supplied oxygen and low humidity. Better results would be achieved by using unhumidified oxygen applied to anterior nose with nasal prongs. |
| Treatment: Other     | Mahalanabis D | Asia   | 2004  | Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe ALRI | Prospective (n = 174). Zinc increased the recovery rate for boys with acute LRTI but not for girls. Vitamin A supplementation had no impact on recovery in boys or girls. |
|                      |           |         |       |                                                                      | Meta-analysis (n = 7 RCTs). No difference in the duration of symptoms or outcomes of LTRI with use of zinc.                                |
|                      | Das RR    | Asia    | 2012  | Short-term therapeutic role of zinc in children <5 years of age hospitalized for severe acute LRTI | Prospective RCT (n = 283). Children with acute LRTI were randomized to adjuvant Vitamin A versus placebo, with no difference between the groups. Vitamin A supplementation in other studies has demonstrated a protective effect for respiratory infections in children. |
|                      |           |         |       |                                                                      | Prospectively (n = 70). 5 days of vitamins E and C did not change recovery time in children admitted with severe ALRI.                      |
|                      | Kjolhede  | Central America | 1995 | Clinical trial of vitamin A as adjuvant treatment for LRTIs          | Prospectively (n = 263). Children with acute LRTI were randomized to adjuvant Vitamin A versus placebo, with no difference between the groups. Vitamin A supplementation in other studies has demonstrated a protective effect for respiratory infections in children. |
|                      |           |         |       |                                                                      | Prospectively (n = 70). 5 days of vitamins E and C did not change recovery time in children admitted with severe ALRI.                      |
|                      | Mahalanabis D | Asia   | 2006  | Antioxidant Vitamins E and C as adjunct therapy of severe acute lower-respiratory infection in infants and young children: A randomized controlled trial | Prospectively (n = 263). Children with acute LRTI were randomized to adjuvant Vitamin A versus placebo, with no difference between the groups. Vitamin A supplementation in other studies has demonstrated a protective effect for respiratory infections in children. |
|                      |           |         |       |                                                                      | Prospectively (n = 70). 5 days of vitamins E and C did not change recovery time in children admitted with severe ALRI.                      |
|                      | Zedan M   | Africa  | 2010  | Montelukast as an episodic modifier for acute viral bronchiolitis: A randomized trial | Prospectively (n = 85). Children with acute bronchiolitis, montelukast reduced length of stay in hospital.                                |
| Treatment: Antibiotics and oxygen | Mishra S | Middle East | 1993 | ARI control program: Results in hospitalized children               | Prospectively (n = 100). Children with severe pneumonia and very severe pneumonia were admitted to a hospital and treated according to WHO guidelines, with penicillin for severe cases and chloramphenicol for severe cases. Oxygen was administered based on respiratory rate. No children with severe pneumonia died, but 3/39 with very severe pneumonia died. When children had suspected staphylococcus, they were treated with gentamicin. 74.3% of children with very severe pneumonia received iv fluids. Congestive heart failure, of unclear clinical definition, was seen in 13 of the patients with very severe pneumonia admitted to the ICU, with ARF responsible for 58.2%. Hospital mortality was 57% compared with 28% for non-HIV patients. Ventilation and high APACHE II score were associated with mortality. Most patients were on bacitracin prophylaxis and HAART, but average CD4 count was below 100 |
|                      |           | Pakistan |       |                                                                      | Prospectively (n = 595). For children with severe pneumonia randomized to co-trimoxazole versus amoxicillin, treatment failure was 33% versus 18% (P = 0.009). In vitro MIC did not predict treatment failure. Treatment failure was also higher in co-trimoxazole group for nonsevere pneumonia, but did not reach statistical significance. |
|                      |           |         |       |                                                                      | Prospectively (n = 889). Children <5 with mild ARI were randomized to supportive care only or supportive care plus amoxicillin. There was no difference in between the two groups regarding cure or progression to moderate ARI, demonstrating that there is no role for antibiotics in mild ARI. |
|                      |           |         |       |                                                                      | Prospectively (n = 789). In a real world implementation of case management of ARI, the community penetration was low, and 75% of the children who died from ARI in the region had not received standard case management. Many parents took their children to RMPs who were not included in training. Children who received antibiotics had very low CFR. 85% of males referred to hospital followed the advice compared with 58% of female children. |

Contd...
Table 4: Contd...

| Author                  | Region | Country    | Year | Title                                                                 | Findings                                                                 |
|-------------------------|--------|------------|------|-----------------------------------------------------------------------|--------------------------------------------------------------------------|
| Likitnukul S            | Asia   | Thailand   | 1994 | Systemic *H. influenzae* disease in Thai children                     | Retrospective (*n* = 50). Patients with systemic *H. influenzae* had 8% mortality. High in vitro resistance to penicillins, chloramphenicol and co-trimoxazole but no resistance to third generation cephalosporins |
| Idoko JA                | Africa | Nigeria    | 1995 | Open clinical trial of roxithromycin among patients of Jos University  | Prospective (*n* = 24). Patients with acute upper respiratory and lower respiratory infections were treated with roxithromycin and 23 had clinic recovery and the drug was well-tolerated throughout. There was no comparison group |
| Gbadero DA              | Africa | Nigeria    | 1995 | Microbial inciters of acute asthma in urban Nigerian children         | Prospective (*n* = 86). Viral upper respiratory infections were frequently identified in children with acute asthma exacerbation. Even in children with fever, viral causes more overwhelming majority. Bacteremia was present in 2 (2.4%) of the children. Routine antibiotics in children with asthma exacerbation is not indicated |
| Sengupta J              | Asia   | India      | 2004 | Comparative evaluation of cefpodoxime versus ceftixime in children    | Prospective (*n* = 776). Children with community acquired pneumonia or acute exacerbation of chronic bronchitis were treated with oral cefpodoxime or oral ceftixime with 97% response with cefpodoxime and 86.8% response with ceftixime. Cefixime does not have good coverage against *Streptococcus* |
| Brent AJ                | Africa | Kenya      | 2006 | Salmonella bacteremia in Kenyan children                              | Retrospective (*n* = 77). A hospital took blood cultures on all admissions and found 166 cases of nontyphoidal Salmonella bacteremia. 46% of these patients met clinical definition of pneumonia and 21% of these patients died. A number of them had not been started on antibiotics or had empirically been started on penicillin monotherapy, which does not cover NTS |
| Rahman M                | Asia   | Bangladesh | 2008 | *H. influenzae* type-b and non-b-type invasive diseases in urban      | Prospective (*n* = 1493). Children with pneumonia, meningitis and sepsis were tested for *H. influenza*. The most common serotype was B. 25/1493 cases of pneumonia had *Haemophilus*, and it was clustered in the children less than a year. Isolates had high resistance to ampicillin, but good sensitivity to ceftriaxone, augmentin, and fluoroquinolones |
| Asghar R                | Multiple | Bangladesh | 2008 | Chloramphenicol versus ampicillin plus gentamicin for community acquired | Prospective RCT (*n* = 958). Children 2-59 months with severe pneumonia were enrolled in RCT comparing chloramphenicol to ampicillin plus gentamicin and found less treatment failure with ampicillin and gentamicin (11% vs. 16%), particularly in patients with *S. pneumonia*. Bacteremia was associated with higher treatment failure with chloramphenicol but not ampicillin plus gentamicin |
| Rijal B                 | Asia   | Nepal      | 2010 | Antimicrobial susceptibility pattern and serotyping of *Streptococcus*  | Prospective (*n* = 3774). 60 isolates of *S. pneumonia* from children in Nepal showed high resistance to cotrimazole but low resistance to penicillin, chloramphenicol and erythromycin. The study did not differentiate pneumonia to other forms of illness |
| Dashti-Khavidaki Rijal S | Middle | Iran       | 2010 | Approach to Pandemic 2009 influenza: first report from a main referral | Prospective cross-sectional (*n* = 434). Suspected cases were evaluated and started empirically on oseltamivir. Based on severity, patients were treated in the community, admitted to the floor or admitted to the ICU. 20/24 patients admitted to the ICU died. Patients were started empirically on antibiotics to cover potential bacterial superinfection |
| Celebri S               | Eastern | Turkey     | 2010 | Colistimethate sodium therapy for MDR isolates in pediatric patients  | Prospective (*n* = 15). Colistimethate sodium was used to treat 15 children with nosocomial MDR infections such as Pseudomonas, primarily VAP. 4 children died and the rest had response to antibiotics |
| Menif K                 | Eastern | Tunisia    | 2011 | Community-associated MRSA infections in a pediatric Intensive Care Unit | Retrospective (*n* = 11). 14 children were admitted to the PICU over ten years with community acquired MRSA. Most (11/14) had pulmonary involvement. Median age 3 months. 2 patients died |
Table 4: Contd...

| Author | Region | Country | Year | Title | Findings |
|--------|--------|---------|------|-------|----------|
| Zaidi AKM | Multiple | - | 2011 | Effect of case management on neonatal mortality due to sepsis and pneumonia | Systematic review ($n=7$). A meta-analysis of studies using oral and injectable antibiotics for neonatal sepsis and pneumonia show mortality benefit. The Delphi method with twenty respondents showed that experts expect injectable to save more lives than oral antibiotics. The studies in meta-analysis represented Nepal, India, Pakistan, and Tanzania. |
| Mosites EM | Multiple | - | 2014 | Care-seeking and appropriate treatment for childhood acute respiratory illness: An analysis of demographic and health survey and multiple indicators cluster survey datasets for high-mortality countries | Cross-sectional survey ($n=17$ countries). Over 66 million children not treated with antibiotics for ALRI in 2010. Treatment is associated with urban residence. Lowest proportion in Africa relative to Asia. |
| Wickramatilake C | Asia | Sri Lanka | 2016 | Are we over prescribing antibiotics in children with acute LRTIs in Sri Lanka? | Descriptive cross-sectional ($n=281$). Children admitted with LRTI, 19% with pneumonia, 98.9% received antibiotics, 71.9% given IV antibiotics, most commonly penicillins but also including cephalosporins and carbapenems. Antibiotics appear to be overused |
| Bhuyan GS | Asia | Bangladesh | 2017 | Bacterial and viral pathogen spectra of ARIs in under-5 children in hospital settings in Dhaka city | Prospective ($n=230$). 200 children with ARHI had nasal swabs for bacterial culture and viral RT-PCR. 21.5% were culture positive compared with 7% of asymptomatic patients. 79% of the patients were positive for viral infection. Some patients were co-infected. Among the bacterial isolates, ceftriaxone had the highest degree of in vitro sensitivity |
| Emerson E | Multiple | -- | 2017 | ARI, diarrhea and fever in young children at-risk of intellectual disability in 24 low- and middle-income countries | Cross-sectional cluster survey. In both low- and middle-income countries children at risk of intellectual disability are more likely to report recent ARI and diarrheal illness and less likely to have received treatment for either |
| Muley VA | Asia | India | 2017 | Study of invasive Pneumococcal infection in adults with reference to Penicillin resistance | Prospective ($n=40$). Cases of invasive pneumococcal disease were analyzed. 15 were pneumonia with pleural effusion. 40% of isolates were resistant to cotrimoxazole but over 90% were sensitive to ciprofloxacin, ceftaxime, and penicillins |
| Mahdi SA | Africa | South Africa | 2000 | Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired LRTIs in HIV Type 1-infected children | Prospective ($n=1434$). 1215 children were admitted with severe pneumonia and all had screening blood cultures. 45% of the children had HIV-1. Children with HIV had higher rates of bacteremia (14.0% vs. 6.5%) and mortality (13.1% vs. 2.1%). There was a higher rate of TB among children with HIV. 6/10 S. aureus in children with HIV was MRSA compared with 0/4 in children without HIV |
| Agarwal R | Asia | India | 2005 | Experience with ARDS caused by TB in a respiratory Intensive Care Unit | Retrospective ($n=187$). 9/187 patients presenting with ARDS to an ICU were ultimately diagnosed with TB but were started on anti TB treatment prior to completion of workup. 2/9 patients died |
| Treatment: Ray MS | Asia | India | 2002 | Comparison of nebulized adrenaline versus salbutamol in wheeze associated respiratory tract infection in infants | Prospective ($n=91$). Children with the 1st or 2nd time wheeze were randomized to adrenaline or salbutamol nebulized. Both drugs resulted in improvement, but adrenaline showed greater improvement and a greater proportion of children were able to be discharged home |
| Treatment: Ojha AR | Asia | Nepal | 2014 | A comparative study on use of 3% saline versus 0.9% saline nebulization in children with bronchiolitis | Prospective RCT ($n=108$). In bronchiolitis, no greater in using nebulized hypertonic saline versus normal saline |
| Treatment: Hussain SF | Asia | Pakistan | 2004 | Non-invasive ventilation in the management of acute respiratory failure in Pakistan | Retrospective ($n=20$). Patients were started on BiPAP. Success with both hypoxic and hypercarbic respiratory failure was over 60%. Pneumonia patients not separated out |
| Kot J | Asia | India | 2010 | Bubble CPAP for respiratory distress syndrome in preterm infants | Retrospective ($n=7$). Infants were more likely to fail CPAP if they had pneumonia/sepsis |
and evaluation were insufficient to measure the quality of the intervention.\textsuperscript{65} Noninvasive ventilation (NIV) is associated with reduced mortality, although no randomized controlled trials exist.\textsuperscript{59-61} A total of 40 patients admitted to the ICU with acute hypoxemic respiratory failure but not immediately intubated were trialed on NIV, and 47.6\% of those patients subsequently required intubation. For a group largely composed of acute respiratory distress syndrome patients, NIV had a high failure rate. The worse the blood gas initially, the higher the risk of subsequent intubation. The authors conclude that although NIV had good outcomes with chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema, patients have to be carefully selected if they have other etiology of respiratory failure.\textsuperscript{66} In Turkey, the following risk factors of late failure of noninvasive mechanical ventilation were found: high APACHE II score, high CRP level, low GCS, low albumin, weak cough, bad compliance to noninvasive mechanical ventilation, the presence of bronchietasis/peptide nucleic acid, and absence of improvement of $\text{PaO}_2/\text{FiO}_2$.\textsuperscript{67}

### Empiric antibiotic choice

International and local treatment guidelines guide choice of empiric antibiotics, as patterns of etiologic agent and sensitivities varies by location. Identifying a specific bacterial etiology for pneumonia via blood cultures, sputum cultures, or even lung aspiration presents delay, low yield, and high cost.\textsuperscript{68} Despite blood cultures on every patient and many patients having bronchoalveolar lavage cultures, only 25\% of patients had a specific infectious pathogen identified. Given this low yield and the delayed results of cultures, treatment has to be started empirically and should reflect the local epidemiology.\textsuperscript{62}

To guide the choice of empiric antibiotics, we need to understand the local burden of various infections and the patterns of drug effectiveness. For instance, in Southeast Asia, sputum cultures of patients with acute COPD exacerbations showed a range of pathogen, including Pseudomonas, depending on the country. Overall, fluoroquinolones showed high susceptibilities and are a good empiric choice.\textsuperscript{66}

Drug effectiveness is different than drug sensitivity, as some strains with \textit{in vitro} resistance show clinical
A total of 300 patients with COPD exacerbation were treated with cefaclor or clarithromycin with similar efficacy. COPD exacerbations are not always bacterial, but antibiotics can produce clinical improvement. Lebanon has published national treatment guidelines depending on the level of severity.

In Tanzania, patients meeting the IMAI criteria for severe pneumonia had investigations that diagnosed etiology in 37% of patients, and among all patients, empiric ceftriaxone had the highest utility, working against known etiology in 17% of patients. Other diseases (cryptococcosis, histoplasmosis, Q fever, Rickettsial diseases) were common and need their specific treatment. A cohort of patients with CAP in France were significantly older with more comorbidities than in Conakry, while those in Conakry were more likely to have initial shock and herpes. Mortality (6% vs. 8%) and clinical recovery (88% vs. 85%) were similar in both settings despite penicillin along being used in the majority of cases in Conakry and multiple or second-line antibiotics being often used in France.

Of 202 isolates of Klebsiella pneumonia, 77.7% produces ESBL. While the study included the majority of urinary specimens, the findings held true for respiratory specimens. Based on individual sensitivity testing, the most widely efficacious antibiotic was imipenem.

A total of 45 patients with lung abscesses were treated over 3 years. Twenty-nine were treated medically and 5 died. Sixteen were treated surgically and six died. Chest radiograph showed air-fluid levels. Sputum culture grew out a single organism in 11 patients. Massive hemoptysis was the primary indication for surgical intervention.

Viral respiratory infections
Viral infections can present with critical illness benefiting from advanced interventions. Sixty-one patients were admitted to ICU in Turkey with H1N1. Mortality was 50.8% overall. Many patients had hypoxemic respiratory failure. Use of noninvasive motion ventilator was associated with increased survival. For patients with influenza, investigators found increased mechanical ventilation requirement in female with pregnancy, diabetes mellitus, hypertension, tachypnea, bilateral lung involvement or involvement of RU/middle/multiple zones, or cardiac involvement.

Other treatments
In addition to antibiotics and respiratory support, adjunctive treatment raises the possibility of improved outcomes. ADAPT-232 a mix of plant extracts speeds the recovery from pneumonia and increases the quality of life during convalescence in a placebo-controlled trial. A meta-analysis of five studies of Vitamin A in acute lower respiratory tract infections showed no difference in recovery or mortality.

DISCUSSION
As noted in the GBD and the WHO literature and reiterated in our review, the burden of critical care illness predominantly affects LMIC, with up 50%–70% of total deaths from conditions that could benefit from the availability of critical care versus <20% in high- and upper-middle-income settings. While intuitively it is often argued that critical care is not practical in low-resource settings, critical illness in ubiquitous and acute care goes beyond ventilators and inotropes. Critical care provision can be simplified into three main components: timely identification of the critically ill, access to and delivery of resources to the acutely ill and definitive management and recovery from illness. This literature review focuses on the three leading causes of death and evidence surrounding acute care in LMICs and demonstrates repeatedly the feasibility in providing acute care in this context.

Timely recognition of illness is of utmost importance to acute care. This is something that must happen outside of intensive care settings likely ICUs and emergency departments as well, including in operating rooms and medical wards, and in the community. Many of the studies noted above focus on timely recognition. For example, in the case of IHD, EKG availability is one limitation while the interpretation of the EKG is another. Some creative solutions, like the one using telemedicine methods in India can make a limited resource, such as a specialist, more feasible. Regarding stroke care, recognition was difficult as well showing that low resource stroke scores and clinical signs were unable to identify hemorrhagic versus ischemic strokes. Other methods if CT scan was unavailable like biomarkers were discussed, but further research would be needed to implement any potentially meaningful change. When CT scan was available there was also discussion of using CTP in addition to better identify patients who might receive thrombolysis when the timing of onset was unknown, but further research is needed here as well. Similarly, many studies were devoted to early recognition of LRIs as well as classification of severity of illness to better triage patients on the need for antibiotics, fluid administration, and a higher level of care (home vs. ward vs. ICU). Multiple studies showed clinical symptoms that can be used to make a diagnosis and severity including the WHO guidelines for pneumonia. Other studies indicated oxygen saturation when available was more useful to diagnose and prognosticate, and the majority of studies indicated that chest X-ray (a limited resource in many settings) was not necessary or useful in identifying or treating a patient. Similarly, with LRI being
so rampant and health-care delivery being limited, many studies looked at whether community health workers or volunteers could be properly trained to recognize LRI and know when to give antibiotics or transfer to a higher level of care and overall showed favorable outcomes.

Access and delivery of care are arguably the most relevant in terms of acute care delivery in LMIC. Things such as transportation to a hospital, available resources at any given care facility, and the amount of personnel, medication, ventilators, ICU beds, etcetera for acute care provision is minimal but also variable across different systems. For example, of 36 low-income studies included in a systematic review in 2015, <50% had any publishable data on ICU resource availability, and of the countries that did have publishable data, the ICU bed per million persons ranged from 1.0 to 16.7. Whenever a treatment or resource is limited, it is important to decide which patients will have the most benefit and certainly avoid it in patients for whom it may cause harm. Outcomes of PCI for example were less favorable when a patient was in cardiogenic shock, possibly highlighting an area for less resource intensive care when there is limited availability. Similarly, the literature above noted that there seemed to be improved functional outcomes for patients with stroke who were in a care-specific stroke ward, but no scoring systems were found to identify which patients might be of most benefit.

Definitive management of a patient and the evidence supporting the treatment varies depending on the context, whether related to the difference in time to care, inherent to the disease processes, epidemiology or other differences. A great example of this is the Fluid Expansion as Supportive Therapy trial in which fluid boluses for septic children in Africa increased mortality, contrary to the evidence of sepsis management to date in developing countries. The best management supported by evidence for acute care in LMICs is largely unknown and this review is the first look at three specific diseases and what is known to date.

Regarding IHD, the literature above repeatedly across different LMIC, finds thrombolytic use and PCI to have favorable outcomes and to be feasible when available but it is limited due to cost, personnel, and delays in recognition of disease as noted. Both medical treatment and thrombolysis require a supply chain for the medications but do not require additional infrastructure. Patients with PCI have good outcomes, and even when performed in a place without cardiothoracic surgery availability, outcomes were favorable. There were minimal reports on CABG or IABP, something done commonly in developed countries, secondary to the lack of resources and availability.

For ischemic CVA, systemic thrombolysis, accepted as a standardized treatment in high- and high-middle-income countries, seems to have increased mortality in studies done in LMIC but more research needs to be done to determine if this is related to diagnosis and timing, poor quality studies or something inherently different in the disease process or care. Less resource intensive and less costly treatments such as atenolol and nimodipine show favorable outcomes for stroke patients as well as subcutaneous heparin for venous thrombosis prophylaxis in intracranial hemorrhage patients. Endovascular techniques to address CVA (outside of subarachnoid hemorrhage) that are more resource intensive but have had hugely positive results in high-resource countries are unstudied in LMICs to date.

In cases of LRI, oxygen therapy is a mainstay of treatment but often unavailable, not to mention noninvasive and invasive ventilation machines. Oxygen therapy did not seem to make a difference in patients with mild disease, NIV was more useful for patients with COPD and CHF components to their disease process and for children rather than adults and actually had an increase in mortality for some adult patients with pneumonia and delayed invasive ventilation. When unavailable, the treatment remains limited to antibiotics, and when required source control from empyema drainage as the mainstays of treatment. There are many studies discussing the different antibiotic resistance patterns and recommended antibiotics depending on epidemiologic or outcome data of patients in different areas as well as different prevalence rates and risk factors for unrecognized HIV, tuberculosis, measles, salmonella, and other atypical pathogens. There are also many studies showing the feasibility of training to avoid the unnecessary antibiotic use and when to give empiric antibiotics. However, research does not exist for all regions, and the correct choice makes a difference between life and death for many people as well as having potential benefit in decreasing overall multidrug-resistant organisms. Many other definitive management choices that remain understudied or unstudied for acute care of IHD, CVA, and LRI in LMICs may have significant effects on morbidity and mortality.

Limitations of this review include the inherent bias from primary studies included in a systematic review. To minimize bias, the methodology of a clear and consistent research question, strict inclusion and exclusion criteria, and three reviewers was used; however, potential bias may be introduced by the exclusion of studies not published in English, French, or Spanish. Furthermore, the majority of studies were from Asia and generalizability may be limited, particularly to Central and South America. In addition to highlight implementable and effective examples, we only included studies with measured quantitative outcomes; as a result, discussion articles and review pieces without quantitative data were excluded. Finally, with any systematic review,
there is the inevitable possibility of “missing” an article however we made a great effort to avoid this by using duplicate screening with multiple reviewers. The purpose of this study was for an expansive review of available literature on the topic, but further study improvement may include a qualitative review of the studies included and a sensitivity analysis to see if any conclusions on best practices might be drawn.

CONCLUSIONS

Acute care of patients with IHD, stroke, and LRI in low-and middle-income countries has been studied. There are many studies demonstrating feasibility and benefit of acute care interventions in these settings including but not limited to percutaneous coronary intervention, stroke-specific ward care, and improved mortality and decreased morbidity in particular patients with oxygen therapy or NIV with LRI. Understanding acute care in these settings is a growing field of interest with increasing recognition of decreased morbidity and mortality as well as increased cost-effectiveness. Further research of critical care interventions in underrepresented LMICs in paramount.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. World Health Organization. The Top 10 Causes of Death: Leading Causes of Death by Economy Income Group; 2015. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/index1.html. [Last accessed on 2018 Apr 09].

2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyанс V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2095-128.

3. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2095-128.

4. Kellermann AL, Razzak JA. Emergency medical care in developing countries: Is it worthwhile? Bull World Health Organ 2002;80:900-5.

5. Obermeyer Z, Abujaber S, Makar M, Stoll S, Kayden SR, Wallis LA, et al. Emergency care in 59 low- and middle-income countries: A systematic review. Bull World Health Organ 2015;93:577-86G.

6. The World Bank. Country and Lending Groups; 2016. Available from: https://www.databank.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. [Last accessed on 2016 Aug 28].

7. Tan JW, Lam CS, Kasim SS, Aw TC, Abanilla JM, Chang WT, et al. Asia-Pacific consensus statement on the optimal use of high-sensitivity troponin assays in acute coronary syndromes diagnosis: Focus on hs-tnI. Heart Asia 2017;9:81-7.

8. Karim MA, Mahmood SF, Akhter J, Qureshi AR. Thrombolytic therapy in acute myocardial infarction in Pakistan. J Pak Med Assoc 1995;45:34-8.

9. Dubey G, Verma SK, Bahl VK. Primary percutaneous coronary intervention for acute ST elevation myocardial infarction: Outcomes and determinants of outcomes: A tertiary care center study from North India. Indian Heart J 2017;69:294-8.

10. Farman MT, Sial IA, Khan NU, Rizvi SN, Saghir T, Zaman KS, et al. Outcome of primary percutaneous coronary intervention at public sector tertiary care hospital in Pakistan. J Pak Med Assoc 2011;61:575-81.

11. Karma C, Oduncu V, Tanalp AC, Erkol A, Dundar C, Srma D, et al. Primary angioplasty in a high-volume tertiary center in Turkey: In-hospital clinical outcomes of 1625 patients. Turk Kardiyol Dern Ars 2011;39:300-7.

12. Moustaghfir A, Haddak M, Mecheche R. Management of acute coronary syndromes in maghreb countries: The ACCESS (Acute coronary events – A multinational survey of current management strategies) registry. Arch Cardiovasc Dis 2012;105:566-77.

13. Sayed S, Fischer S, Karkch M, Hassouna A, Haverich A. Effect of different preoperative patient characteristics on coronary surgery outcome: A comparative study between a developing and a developed country. J Card Surg 2009;24:275-80.

14. Patel SP, Pena ME, Babcock CL. Cost-effectiveness of noninvasive ventilation for chronic obstructive pulmonary disease-related respiratory failure in Indian hospitals without ICU facilities. Lung India 2015;32:549-56.

15. de Andrade L, Lynch C, Carvalho E, Rodrigues CG, Visossi JR, Passos GF, et al. System dynamics modeling in the evaluation of delays of care in ST-segment elevation myocardial infarction patients within a tiered health system. PLoS One 2014;9:e103577.

16. Gupta S, Dewan S, Kausal A, Seth A, Narula J, Varma A, et al. EICU reduces mortality in STEMI patients in resource‑limited areas. Glob Heart 2014;9:425-7.

17. Constantine GR, Herath JJ, Chang AA, Suganthan P, Hewamane BS. Time delay to thrombolytic therapy – A Sri Lankan perspective. Postgrad Med J 1998;74:405-7.

18. Suraseranivongse S, Chawaruechai T, Saengsung P, Komoltri C. Outcome of cardiopulmonary resuscitation in a 2300-bed hospital in a developing country. Resuscitation 2006;71:188-93.

19. Jahic E. Experience and outcomes of primary percutaneous coronary intervention for patients with ST-segment elevation myocardial infarction of tertiary care center in Bosnia and Herzegovina. Med Arch 2017;71:183-7.

20. Okuyen E, Uslu A, Levent MO, Sahin A, Dinckal MH. Caring of ST-elevation myocardial infarction patients in rural community hospital settings: Determinants of in-hospital mortality. Aust J Rural Health 2010;18:173-8.

21. Kaul UA, Verma R, Garg KC. Early intervention with propranolol after acute myocardial infarction: Serial left ventricular function determined and its complications: An ex-post facto study. Glob J Health Sci 2006;8:139.
El Sayed MJ, El Zahran T, Tamim H. Acute stroke care and thrombolytic therapy. Int J Cardiol 1999;69:209-16.

Perikhanian A. Effectiveness and cost-effectiveness of coronary artery bypass surgery versus drug eluting stents in Armenia: A feasibility study. Georgian Med News 2011;6:44-51.

Güer O, Kurbaj A, Işık O. Left anterior descending artery revascularization in low-risk patients: Early outcomes after off-pump versus on-pump surgery. Heart Surg Forum 2011;14:E309-12.

Sokullu O, Aydemir NA, Kurc E, Oray B, Bilgen F, Demirtas M, et al. Emergency management for critical left main coronary artery stenosis. Heart Surg Forum 2011;14:E12-7.

Subban V, Gnanaraj A, Gomathi B, Janakiraman E, Pandurangi U, Kalidoss L, et al. Percutaneous coronary intervention in cardiogenic shock complicating acute ST-elevation myocardial infarction—a single centre experience. Indian Heart J 2012;64:152-8.

Dar MI, Manan AU, Rashheed B, Murtaza G, Ahmad M. Outcome of patients after coronary artery bypass grafting in cardiogenic shock. Ann Thorac Cardiovasc Surg 2007;13:247-50.

Balcı KG, Balcı MM, Şen F, Akboğa MK, Kalender E, Yılmaz S, et al. Results of treatment methods in cardiac arrest following coronary artery bypass grafting. J Card Surg 2009;24:227-33.

Guney MR, Ketenci B, Yapıcı E, Sokullu O, Firat MF, Uyar E, et al. Treatment outcomes of patients treated with noninvasive ventilation in acute hypoxemic respiratory failure. Intensive Care Med 2013;39:439-47.

Subban V, Lakshmanan A, Victor SM, Pakshirajan B, Udayakumaran K, Gnanaraj A, et al. Outcome of primary PCI – An Indian tertiary care center experience. Indian Heart J 2014;66:25-30.

Dharma S, Dakota I, Firdaus A, Wardeh AJ, Jukema JW. The use of intra-aortic balloon pump in a real-world setting: A comparison between survivors and non-survivors from acute coronary syndrome treated with IABP. The Jakarta acute coronary syndrome registry. Int J Angiol 2013;22:213-22.

Jafary FH, Khan SA, Kumar H, Malik NF, Kazmi KA, Dhakam S, et al. Survival of patients treated with intra-aortic balloon counterpulsation at a tertiary care center in Pakistan – Patient characteristics and predictors of in-hospital mortality. BMC Cardiovasc Disord 2004;4:22.

Kazmi WH, Rashheed SZ, Ahmed S, Saadat M, Altaf S, Samad A, et al. Noninvasive therapy for the management of patients with advanced coronary artery disease. Corron Artery Dis 2012;23:549-54.

Kochar DK, Joshi A, Aggarwal N, Aseri S, Sharma BV, Aggarwal TD, et al. Poor diagnostic accuracy and applicability of Siriraj stroke score, Allen score and their combination in differentiating acute haemorrhagic and thrombotic stroke. J Assoc Physicians India 2000;48:584-8.

Man K, Karem AM, Ahmad Alias NA, Shuaib IL, Tharakan J, Abdullah JM, et al. Computed tomography perfusion of ischemic stroke patients in a rural Malaysian tertiary referral centre. Singapore Med J 2006;47:77.

Mihalka L, Smolanka V, Bulecza R, Mulesa S, Bereczki B, et al. A population study of stroke in West Ukraine: Incidence, stroke services, and 30-day case fatality. Stroke 2001;32:2227-31.

Scheglov DV, Polischuk ME, Scheglov VI, Mamonova MY, Monsein LJH. Endovascular treatment of vasospasm related to acute subarachnoid hemorrhage from ruptured aneurysms. Acta Neurochirurg Suppl 2015;120:223-9.

El Sayed MJ, El Zahran T, Tamim H. Acute stroke care and thrombolytic therapy use in a tertiary care center in Lebanon. Emerg Med Int 2014;2014:438737.

Wasay M, Barahi H, Malik A, Yousuf A, Awan S, Kamal AK, et al. Use of endovascular surgery and effect of thrombolysis on acute stroke in Pakistan. Neurosci Res 2010;71:223-5.
bronchitis (B3M-PK-AJBG). J Pak Med Assoc 2003;53:338-45.
72. Moghnieh R, Yared Sakr N, Kanj SS, Musharrafieh U, Husni R, Jradeh M, et al. The lebanese society for infectious diseases and clinical microbiology (LSIDCM) guidelines for adult community-acquired pneumonia (Cap) in Lebanon. J Med Liban 2014;62:40-7.
73. Rubach MP, Maro VP, Bartlett JA, Crump JA. Etiologies of illness among patients meeting integrated management of adolescent and adult illness district clinician manual criteria for severe infections in Northern Tanzania: Implications for empiric antimicrobial therapy. Am J Trop Med Hyg 2015;92:454-62.
74. Sow O, Frechet M, Diallo AA, Soumah S, Conde MK, Diot P, et al. Community acquired pneumonia in adults: A study comparing clinical features and outcome in Africa (Republic of Guinea) and Europe (France). Thorax 1996;51:385-8.
75. Mehrgan H, Rahbar M, Arab-Halvaii Z. High prevalence of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in a tertiary care hospital in Tehran, Iran. J Infect Dev Ctries 2010;4:132-8.
76. Adebonojo SA, Osinowo O, Adebo O. Lung abscess: A review of three-years’ experience at the university college hospital, Ibadan. J Natl Med Assoc 1979;71:39-43.
77. Borse RT, Kadam DB, Sangle SA, Basavraj A, Prasad HB, Umarji PB, et al. Comparison of demographic, clinical, radiological characteristics and comorbidities in mechanically ventilated and nonventilated, adult patients admitted in ICU with confirmed diagnosis of influenza A (H1N1). J Assoc Physicians India 2013;61:887-93.
78. Narimanian M, Badalyan M, Panosyan V, Gabrielyan E, Panossian A, Wikman G, et al. Impact of Chisan (ADAPT-232) on the quality-of-life and its efficacy as an adjuvant in the treatment of acute non-specific pneumonia. Phytomedicine 2005;12:723-9.
79. Brown N, Roberts C. Vitamin A for acute respiratory infection in developing countries: A meta-analysis. Acta Paediatr 2004;93:1437-42.
80. Murthy S, Adhikari NK. Global health care of the critically ill in low-resource settings. Ann Am Thorac Soc 2013;10:509-13.
81. Lim A. Understanding Global Critical Care [podcast]. Maryland CC Project, Editor; 2017.
82. Murthy S, Leligidowicz A, Adhikari NK. Intensive Care Unit capacity in low-income countries: A systematic review. PLoS One 2015;10:e0116949.
83. Maitland K, Babiker A, Kiguli S, Molyneux E; FEAST Trial Group. The FEAST trial of fluid bolus in African children with severe infection. Lancet 2012;379:613.
# Appendix A: List of search terms used for systematic review

| Type of search term | Search terms |
|---------------------|--------------|
| Search Term 1: Emergency term | (“Critical Care” [Mesh] OR “critical care”) OR (“Resuscitation” [Mesh] OR resuscitation) OR (“Critical Illness”[Mesh] OR “critical illness”) OR (“Acute Disease” [Mesh] OR “acute disease”) OR (“Emergency Medicine” [Mesh] OR “emergency medicine”) OR (“Emergency Treatment” [Mesh] OR “emergency treatment”) OR (“acute disease” [Mesh] OR “acute disease”) OR (“Sepsis” [Mesh] OR “Sepsis”) OR (“shock” [Mesh] OR “shock ”) |
| Search Term 2: Diagnosis term | (“Ischemic heart disease” [Mesh] OR Ischemic heart disease) OR (“Ischaemic heart disease” [Mesh] OR Ischaemic heart disease) OR (“Acute coronary syndrome” [Mesh] OR Acute coronary syndrome) OR Acute Myocardial Ischemia OR Acute Myocardial Infarction OR Ischemic Heart Disease OR Coronary Artery Disease OR Coronary Arteriosclerosis OR Coronary Arterioscleroses OR Coronary Atherosclerosis OR Coronary Atherosclerotic OR (“Cerebrovascular Disorders” [Mesh] OR cerebrovascular disease) OR (“Cerebrovascular accident” [Mesh] OR cerebrovascular accident) OR (“stroke” [Mesh] OR “stroke”) OR Cerebrovascular Accidents OR CVA OR CAVas OR Cerebrovascular Apoplexy OR Apoplexy OR Cerebrovascular Stroke OR Cerebrovascular Strokes OR Brain Vascular Accident OR Brain Vascular Accidents OR Cerebral Stroke OR Cerebral Strokes OR Acute Stroke OR Acute Strokes OR Acute Cerebrovascular Accident OR Acute Cerebrovascular Accidents OR Cerebrovascular Disorder OR Intracranial Vascular Disorders OR Intracranial Vascular Disorder OR Intracranial Vascular Disease OR Intracranial Vascular Diseases OR Brain Vascular Disorders OR Brain Vascular Disorder OR Cerebrovascular Occlusion OR Cerebrovascular Occlusions OR Cerebrovascular Insufficiency OR Cerebrovascular Insufficiencies OR (“lower respiratory tract infection”[Mesh] OR “lower respiratory tract infection”) OR (“pneumonia”[Mesh] OR “pneumonia”) OR Respiratory Tract Infection OR Respiratory Infection OR Respiratory Infections OR Pneumonia OR Pneumonias OR Pneumonitis OR Pneumonitis OR Pneumonia OR Respiratory Insufficiency OR Respiratory Failure OR Respiratory Depression OR Ventilatory Depression |
| Search Term 3: LMIC term | Search 3 (total): (((“Kosovo” [Mesh] OR kosovo) OR (“Kyrgyzstan” [Mesh] OR “kyrgyz republic”) OR “Kyrgyzstan”) OR (“Laos” [Mesh] OR “laos” or “laos”) OR (“Lesotho” [Mesh] OR lesotho) OR (“Mauritania” [Mesh] OR mauritania) OR (“Micronesia” [Mesh] OR “federated states of micronesia”) OR microeas) OR (“Moldova” [Mesh] OR moldova) OR (“Morocco” [Mesh] OR morocco) OR (“Myanmar” [Mesh] OR myanmar) OR (“Nicaragua” [Mesh] OR nicaragua) OR (“Nigeria” [Mesh] OR nigeria) OR (“Pakistan” [Mesh] OR pakistan) OR (“Papua New Guinea”[Mesh] OR “papua new guinea”) OR (“Philippines” [Mesh] OR philippines) OR (“Samoa” [Mesh] OR “samo” OR (“Atlantic Islands” [Mesh] OR “sao tome” OR “principe”) OR (“Senegal” [Mesh] OR senegal) OR (“Melanesia” [Mesh] OR “solomon islands”) OR (“Sri Lanka” [Mesh] OR “sri lanka”) OR (“Sudan” [Mesh] OR sudan) OR (“Swaziland” [Mesh] OR swaziland) OR (“Syria” [Mesh] OR “syrian arab republic”) OR (“Tajikistan” [Mesh] OR tajikistan) OR (“East Timor”[Mesh] OR “timor-leste” OR “timor leste” OR “east timor”) OR (“Ukraine”[Mesh] OR Ukraine) OR (“Uzbekistan” [Mesh] OR “uzbekistan”) OR (“Vanuatu” [Mesh] OR vanuatu) OR (“Middle East” [Mesh] OR “west bank” OR gaza) OR (“Yemen” [Mesh] OR “yemen”) OR (“Zambia”[Mesh] OR “zambia”) OR (“Micronesia”[Mesh] OR Kiribati) OR (“Kenya” [Mesh] OR kenya) OR (“Indonesia” [Mesh] OR “indonesia”) OR (“India” [Mesh] OR “india”) OR (“Honduras” [Mesh] OR “honduras”) OR (“Guyana” [Mesh] OR “guyana”) OR (“Guatemala” [Mesh] OR “guatemala”) OR (“Ghana” [Mesh] OR “ghana”) OR (“Georgia (Republic)” [Mesh] OR “georgia”) OR (“El Salvador” [Mesh] OR “el salvador”) OR (“Egypt”[Mesh] OR “egypt”) OR (“arab republic of egypt”) OR (“Djibouti”[Mesh] OR djibouti) OR (“Cote d’Ivoire” [Mesh] OR “cote d’ivoire”) OR (“Congo” [Mesh] OR congo) OR (“Cameroon” [Mesh] OR “cameroon”) OR (“Cape Verde” [Mesh] OR “cape verde”) OR (“Bolivia” [Mesh] OR “bolivia”) OR (“Bhutan” [Mesh] OR “bhutan”) OR (“Bangladesh” [Mesh] OR “bangladesh”) OR (“Armenia” [Mesh] OR “armenia”) OR (“Zimbabwe” [Mesh] OR “zimbabwe”) OR (“Uganda” [Mesh] OR “uganda”) OR (“Togo” [Mesh] OR “togo”) OR (“Tanzania” [Mesh] OR “tanzania”) OR (“Sudan” [Mesh] OR “sudan”) OR (“south sudan”) OR (“Sierra Leone” [Mesh] OR “sierra leone”) OR (“Rwanda”[Mesh] OR “rwanda”) OR (“Niger” [Mesh] OR “niger”) OR (“Nepal” [Mesh] OR “nepal”) OR (“Mozambique” [Mesh] OR “mozambique”) OR (“Somalia” [Mesh] OR “somalia”) OR (“Myanmar” [Mesh] OR “myanmar”) OR (“Nicaragua” [Mesh] OR “nicaragua”) OR (“Nigeria” [Mesh] OR “nigeria”) OR (“Pakistan” [Mesh] OR “pakistan”) OR (“Papua New Guinea”[Mesh] OR “papua new guinea”) OR (“Philippines” [Mesh] OR “philippines”) OR (“Samoa” [Mesh] OR “samo” OR (“Atlantic Islands” [Mesh] OR “sao tome” OR “principe”) OR (“Senegal” [Mesh] OR “senegal”) OR (“Melanesia” [Mesh] OR “solomon islands”) OR (“Sri Lanka” [Mesh] OR “sri lanka”) OR (“Sudan” [Mesh] OR “sudan”) OR (“Swaziland” [Mesh] OR “swaziland”) OR (“Syria” [Mesh] OR “syrian arab republic”) OR (“Tajikistan” [Mesh] OR “tajikistan”) OR (“East Timor”[Mesh] OR “timor-leste” OR “timor leste” OR “east timor”) OR (“Ukraine”[Mesh] OR “ukraine”) OR (“Uzbekistan” [Mesh] OR “uzbekistan”) OR (“Vanuatu” [Mesh] OR “vanuatu”) OR (“Middle East” [Mesh] OR “west bank” OR “gaza”) OR (“Yemen” [Mesh] OR “yemen”) OR (“Zambia”[Mesh] OR “zambia”) OR (“Micronesia”[Mesh] OR “kiribati”) OR (“Kenya” [Mesh] OR “kenya”) OR (“Indonesia” [Mesh] OR “indonesia”) OR (“India” [Mesh] OR “india”) OR (“Honduras” [Mesh] OR “honduras”) OR (“Guyana” [Mesh] OR “guyana”) OR (“Guatemala” [Mesh] OR “guatemala”) OR (“Ghana” [Mesh] OR “ghana”) OR (“Georgia (Republic)” [Mesh] OR “georgia”) OR (“El Salvador” [Mesh] OR “el salvador”) OR (“Egypt” [Mesh] OR “egypt”) OR (“arab republic of egypt”) OR (“Djibouti” [Mesh] OR “djibouti”) OR (“Cote d’Ivoire” [Mesh] OR “cote d’Ivoire”) OR (“Congo” [Mesh] OR “congo”) OR (“Cameroon” [Mesh] OR “cameroon”) OR (“Cape Verde” [Mesh] OR “cape verde”) OR (“Bolivia” [Mesh] OR “bolivia”) OR (“Bhutan” [Mesh] OR “bhutan”) OR (“Bangladesh” [Mesh] OR “bangladesh”) OR (“Armenia” [Mesh] OR “armenia”) OR (“Zimbabwe” [Mesh] OR “zimbabwe”) OR (“Uganda” [Mesh] OR “uganda”) OR (“Togo” [Mesh] OR “togo”) OR (“Tanzania” [Mesh] OR “tanzania”) OR (“Sudan” [Mesh] OR “sudan”) OR (“south sudan”) OR (“Sierra Leone” [Mesh] OR “sierra leone”) OR (“Rwanda”[Mesh] OR “rwanda”) OR (“Niger” [Mesh] OR “niger”) OR (“Nepal” [Mesh] OR “nepal”) OR (“Mozambique” [Mesh] OR “mozambique”) OR (“Somalia” [Mesh] OR “somalia”) |